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CONTENTS OF PREVIOUS NUMBERS

SEPTEMBER, 1923. NUMBER 3

The Vital Capacity of the Chinese: An Occupational Study. John H. Foster, M.D., and P. L. Hsieh, M.D., Changsha, China.

Blood Sugar Reaction Following Intravenous Injection of Glucose. L. G. Rigler, M.D., and H. L. Ulrich, M.D., Minneapolis.

Experiments with Hodgkin's Disease: An Attempt to Produce It in Anthropoids and Other Monkeys. W. F. Cunningham, M.D., and Kenneth McAlpin, M.D., New York.

The Size of the Heart in Pneumonia: A Teleroentgenographic Study, with Observations on the Effect of Digitalis Therapy. Robert L. Levy, M.D., New York.

Definition of Hemolytic Streptococcus Parasitism in the Upper Air Passages of Healthy People. Arthur L. Bloomfield, M.D., and Augustus R. Felty, M.D., Baltimore.

Studies of Liver Function: Rose Bengal Elimination from the Blood as Influenced by Liver Injury. G. D. Delprat, Jr., San Francisco.

Sensitization Tests with Digestive Products of Protein. I. Chandler Walker, M.D.; Arthur S. Wetmore, and June Adkinson, Boston.

The Mechanism of Production of Breath Sounds. P. Martini, M.D., Munich, Germany.

The Basal Metabolism During Pregnancy and the Puerperium. Howard F. Root, M.D., and Hester K. Root, Boston.

Toxic Nephritis in Pyloric and Duodenal Obstruction: Renal Insufficiency Complicating Gastric Tetany. George E. Brown, M.D.; George B. Eusterman, M.D.; Howard R. Hartman, M.D., and Leonard G. Rowntree, M.D., Rochester, Minn.

A Clinical Report on Acute Cases of Mercuric Chlorid Poisoning. L. C. Gatewood, M.D., and Arthur F. Byfield, M.D., Chicago.

Studies in Familial Neurosyphilis. III. Conjugal Neurosyphilis (Second Communication). Joseph Earle Moore, M.D., and Jarold E. Kemp, M.D., Baltimore.

OCTOBER, 1923. NUMBER 4

Bacteriologic Observations on Acute Tonsillitis with Reference to Epidemiology and Susceptibility. Arthur L. Bloomfield, M.D., and Augustus R. Felty, M.D., Baltimore.

Electrocardiographic Changes Following Occlusion of the Left Coronary Artery. Fred M. Smith, M.D., Chicago.

Studies on the Rabbit's Heart. I. Effect of Strophanthin on the Size of the Normal and of the Abnormal Heart. G. F. Strong, M.D., Vancouver, B.C., and Burgess Gordon, M.D., Spokane, Wash.

Studies on the Rabbit's Heart. II. Effect of Vigorous Exercise on the Size of the Normal and the Abnormal Heart. Burgess Gordon, M.D., Spokane, Wash., and G. F. Strong, M.D., Vancouver, B.C.

Giardia Interstinalis Infection. Edward Hollander, M.D., New York.

Malignant Lymphoma (Hodgkin's Disease). A Radiographic Study. Lester R. Whitaker, M.D., Cambridge, Mass.

Gonorrheal Myelitis. Frank M. Phifer, M.D., and N. K. Forster, M.D., Chicago.

Clinical and Roentgenologic Study of One Hundred and Five Cases of Syphilis with Reference to the Cardiovascular System. Edward Steinfeld, M.D.; George E. Pfahler, M.D., and Joseph V. Klauder, M.D., Philadelphia.

The Influenza Epidemic at Camp Devens in 1918: A Study of the Pathology of the Fatal Cases. S. Burt Wolbach, M.D., and Channing Frothingham, M.D., Boston.

Observations on Changes in the Size and Shape of Hearts During the Progress of Compensation. J. C. Friedman, M.D., and Sidney Strauss, M.D., Chicago.

Observations on the Influence of Pituitary Extract on the Metabolism in Diabetes Insipidus. James P. Weir, M.D., Rochester, Minn.

Gastroscopy in Thirty Cases of Gastric Neoplasm. E. Schindler, Munich, Germany.

NOVEMBER, 1923. NUMBER 5

General Relation Between Susceptibility and Physiologic Condition. C. M. Child, M.D., Chicago.

General Observations on the Dynamics of Ventricular Systole. I. Auricular Fibrillation. L. N. Katz, M.D., and H. S. Feil, M.D., Cleveland.

Lamblia (Giardia) Infection Associated with Cholecystitis. Report of a Case Treated with Neo-Arsphenamin. J. L. Kanter, M.D., New York.

A Study of the Basal and Nitrogenous Metabolism in a Case of Acute Leukemia During Roentgen-Ray Treatment. W. G. Lennox, M.D., and J. H. Means, M.D., Boston.

Melanuria Without Melanosarcoma: Report of a Case. J. P. Peters, M.D., New Haven, Conn.

The Value of the Electrocardiograph in Prognosis. W. A. Bloedorn, M.D., and L. J. Roberts, M.D., Washington, D.C.

Gastric Ulcer and Achlorhydria. J. R. Bell, M.D., London, Eng.

Experimental Infectious Streptococcus Endocarditis and Its Arsenical Therapy (Sodium Cacodylate). J. A. Bargen, M.D., Chicago.

The Complications of Staphylococcus Focal Infections. Laird M. Morris, M.D., San Francisco.

A Contribution to the Biochemistry and Treatment of Chronic Nephrosis (Epstein). I. M. Rabinowitch, M.D., and M. C. C. Childs, M.D., Montreal, Canada.

A Study of the Blood Oxygen in Diabetes Mellitus. S. B. Grant, M.D., Boston.

Gastric Secretion in Response to Duodenal Feeding. A. L. Garbat, M.D., New York.

Digitalis Elimination. Harry Gold, M.D., New York.

Observations on the Effects of Insulin in the Treatment of Diabetes Mellitus. I. M. Rabinowitch, M.D., Montreal, Canada.

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THE IMPORTANCE OF OUR KNOWLEDGE OF THYROID PHYSIOLOGY IN THE CONTROL OF THYROID DISEASES *

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NEW YORK

Physiology of the Thyroid

When we realize that our definite knowledge of the function of the thyroid gland dates from 1874, when Sir William Gull published his clinical pathological study, "On a Cretinoid State Supervening in Adult Life in Women," all will agree that much progress has been made during the nearly fifty years that we have followed its publication. While today we can boast that we are able to reproduce experimentally, to diagnose, and to treat myxedema successfully, and that we can with certainty prevent endemic goiter and endemic cretinism, it must still be admitted that our knowledge of the rôle of the thyroid gland in human physiology and pathology is yet in its infancy. Our lack of knowledge concerning the thyroid applies particularly to its influence on other glands of internal secretion and their influence on it. We probably possess a more detailed knowledge of the anatomy, physiology, chemistry and pathology of the thyroid than of any other gland, and I shall attempt to review as briefly as possible some of the more important facts of thyroid physiology and their application to the problem of the control of thyroid disease.

The major function of the thyroid, as we now know it, is to provide a means through its iodin-containing hormone for maintaining a higher rate of metabolism than would otherwise exist and for varying this rate. The gland is not essential for the vegetative life of adult animals. In the young it is necessary for growth and differentiation. Thyroid removal in animals causes a lowering of metabolism (measured as heat production) as much as 40 per cent., which is comparable to the maximum decrease seen in the severest forms of human myxedema. This decrease in metabolism begins usually on the sixth or seventh day after removal, and in cats and rabbits reaches its maximum about the twentieth day after removal, as shown in Figure 1. The reduction in metabolism is permanent if the thyroid is completely removed, but if,

* Eighth Mellon lecture delivered before the Society for Biological Research, University of Pittsburgh, May 10, 1923.

as usually happens, fragments or accessories remain, regeneration occurs and the metabolism rises again, in some instances, to normal. We have observed rabbits in which the metabolism has remained 20 and 30 per cent. below normal for three years or approximately one half the average life of this animal.

That the thyroid gland provides the means for varying the rate of heat production can be shown in several ways. First, it has been shown in animals that sufficient but sublethal injury to the suprarenal glands causes a marked chronic increase in heat production, provided the thyroid gland is intact; but thyroid removal prior to injuring the

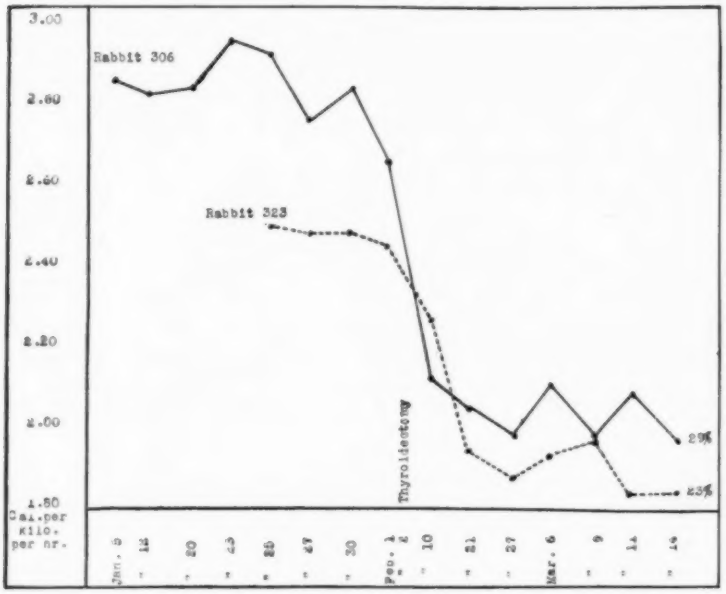


Fig. 1.—Thyroidectomy and heat production.

suprarenal glands greatly reduces or abolishes the increase. Secondly, in all mammals studied there is a marked rise in heat production during pregnancy and lactation. In the rabbit, this increased heat production begins about the middle of pregnancy and continues through the period of lactation. Thyroidectomy in the rabbit abolishes or greatly reduces this normal rise in metabolism. This relation of the thyroid to the increased heat production of pregnancy and lactation probably has an important bearing on thyroid enlargements (goiters) occurring during pregnancy and lactation and will be referred to again. Thirdly, the administration of thyroid glands, as first shown by Magnus-Levy in

1895, causes a striking increase in heat production. Fourthly, thyroid removal causes a decrease in heat production. These facts constitute sufficient evidence that the thyroid plays an important part not only in the maintenance of a given basal rate of metabolism but also in providing a means, through fluctuation in its activity, for varying this rate. There is some evidence also that the thyroid is an important factor in the increased heat production accompanying bacterial infections.

Magnus-Levy, in 1895, showed that in Gull's disease heat production was decreased, while in exophthalmic goiter it was increased. Also in 1895, Baumann announced that iodin was a normal constituent of the thyroid, and subsequent work has established the fact that the thyroid exerts its influence on metabolism by means of the very stable iodin containing hormone which Kendall in 1916 isolated in crystalline form and gave the name thyroxin. This hormone is intimately associated with the globulin of the colloid, from which it is separated only by destructive hydrolysis, and is stored in the colloid material of the alveoli in variable amounts. The colloid or globulin appears to act as a vehicle for storing the reserve of this very active hormone. Measured as iodin, the maximum store in the normal human thyroid is around 25 mg., or approximately 1 mg. per gram of fresh gland. The thyroid gland has an extraordinary affinity for iodin both in vitro and in vivo. The iodin content may be increased several hundred per cent. within five minutes after the injection of 50 mg. of potassium iodid into the femoral vein of a dog. The administration of iodin in any form in any manner causes the store to be increased to the maximum. This is true for the human thyroid as well. Such rapidly stored iodin is at first inactive, but the transformation to the active form can be demonstrated in dogs in about twenty-four hours by means of the tadpole test. The fact that there is no fixed ratio between the active and the inactive iodin probably indicates that the active iodin is slowly elaborated from the inactive iodin taken from the blood stream and either discharged into the circulation or stored in the colloid.

The functional activity of the gland is controlled chemically mainly through the blood stream but perhaps also indirectly through the sympathetic nervous system. The functional capacity of the gland is not impaired by sectioning the nerves running in the adventitial coats of the vessels and encasing the gland in paraffin. Thyroid tissue autotransplanted in any part of the body shows the same capacity for hyperplasia, involution and the storage of iodin as is exhibited by the normal gland. If bits of the thyroid are removed from the neck and transplanted into the ear, the abdominal wall, and the ovary, these transplants show morphologic and chemical changes similar to those occurring in the nontransplanted tissue. Thus, if the nontransplanted thyroid tissue is undergoing hyperplasia, the transplants, wherever

located, show hyperplasia of similar degree, and if iodin is administered the transplants show the same involution and storage of iodin as occur in the nontransplanted gland.

The thyroid gland exhibits great variations in functional activity to meet the wide variations in metabolism occurring during the life of the animal, particularly in the female. For example, there are variations due to season. Seidell and Fenger have shown the increase in the iodin store during the summer months and its decrease during the late winter and early spring months. Many observers have noted the increased incidence of thyroid enlargement (goiter) during the winter and spring months. There is a notable increase in thyroid activity at puberty, during pregnancy and lactation, during the menopause, during protracted febrile reactions (tuberculosis and syphilis), and following the prolonged use of certain diets, particularly those with a high fat and protein content. It might be pointed out that these conditions, in which the thyroid activity is known to be increased, correspond as regards time to the periods in life when thyroid enlargement or goiter develops. Increased thyroid activity is associated with a decrease in the iodin store in the gland, provided the intake of iodin at such times is not correspondingly increased, and if the iodin store falls below 0.1 per cent., thyroid enlargement begins. The morphologically normal thyroid contains on the average about 0.2 per cent. iodin. The maximum store is between 0.5 and 0.6 per cent. and the minimum store associated with normal gland structure is about 0.1 per cent. The thyroid gland is endowed with an enormous capacity for growth, which provides a factor of safety and a compensatory mechanism to meet increased functional demands. These enlargements of the thyroid are familiar to all of us as ordinary goiter.

In comparing the microscopic appearance and the iodin content of the thyroid glands of several hundred dogs and of human beings, a striking relationship between the iodin store and the histologic structure was made out. In the thyroids with normal structure the iodin content varied between 5.5 mg. and 1 mg. per gram of dried gland. When the iodin store was below 0.1 per cent, hypertrophic and hyperplastic changes were regularly found. In comparing further the varying degrees of thyroid hyperplasia with the iodin store of such glands, it was found that the iodin store progressively decreased as the degree of hyperplasia increased, so that in the most marked hyperplasias, iodin was usually absent or present only in traces. A similar relationship between the iodin store and the histologic structure of the gland has been observed in large series of thyroid glands of ox, pig, sheep and fowl. The generalization may therefore be made that the iodin store varies inversely with the degree of active hyperplasia, and that if the iodin store is higher than 0.1 per cent., no hypertrophic changes are present.

This generalization could readily be tested experimentally by studying the effects of administering and withholding iodin after partial removal of the thyroid. As has been shown by many observers, notably by Wagner, Halsted and Ribbert, if one half to three quarters of the gland is removed, the remainder undergoes compensatory hyperplasia histologically identical with the spontaneous hyperplasias seen in developing goiters. Marine and Lenhart have carried out large numbers of experiments of partial removal, comparing the histologic appearance and iodin store, and it was found that compensatory hyperplasia did not begin until the iodin store in the remaining part had fallen below 0.1 per cent., and that the degree of compensatory hyperplasia increased proportionately as the iodin store decreased, just as was found in the spontaneous hyperplasias. Conversely, if one removes as much as three fourths of the gland and administers traces of iodin (from 1 to 2 mg. weekly), no compensatory hyperplasia takes place in the remaining portion such as would regularly occur if iodin was withheld. The administration of desiccated thyroid will protect the thyroid against compensatory hyperplasia even after the removal of five sixths of the gland. These very simple experiments show clearly that the changes in the iodin store and histologic structure occurring in experimentally controlled hyperplasia are identical with those occurring in spontaneous hyperplasia or goiter.

The same general reaction of the thyroid can also be produced in experimental congenital goiter. The late Professor Halsted first experimentally produced congenital goiter in dogs in 1889. He observed that the puppies born from mothers that had had most of the thyroid gland removed had enlarged actively hyperplastic glands, reaching twenty times the normal size. He noted also that the histologic appearance of such congenital goiters was identical with the compensatory hyperplasia following partial removal of the gland. The fact that removal of most of the thyroid from the mother ordinarily causes marked enlargement of the fetal thyroid has been confirmed from many sources and for many of the experimental laboratory animals, including the dog, the cat, the sheep and the rat. In addition to confirming Halsted's observations on these animals, we have added the additional fact that if one gives a few milligrams of iodin during pregnancy to cats and dogs from which most of the thyroid has been removed, the young at birth will have thyroids normal as to weight, histologic structure and iodin content. We have also been able to obtain from the same animal alternate litters of goiterous and nongoiterous young, merely by withholding or administering iodin. These experimental congenital thyroid hyperplasias are true congenital goiters. They are identical with the spontaneous congenital goiters of man and animals and are dependent on a maternal functional insufficiency of the thyroid. As in many other

instances, the experimental production of congenital goiter merely confirmed the views of the older students of congenital goiter in man, based on their clinical observations.

A litter of four typical congenital cretins were brought to the laboratory at the age of 6 weeks, November 16, 1908. All had marked thyroid enlargement. The accompanying illustrations show the typical

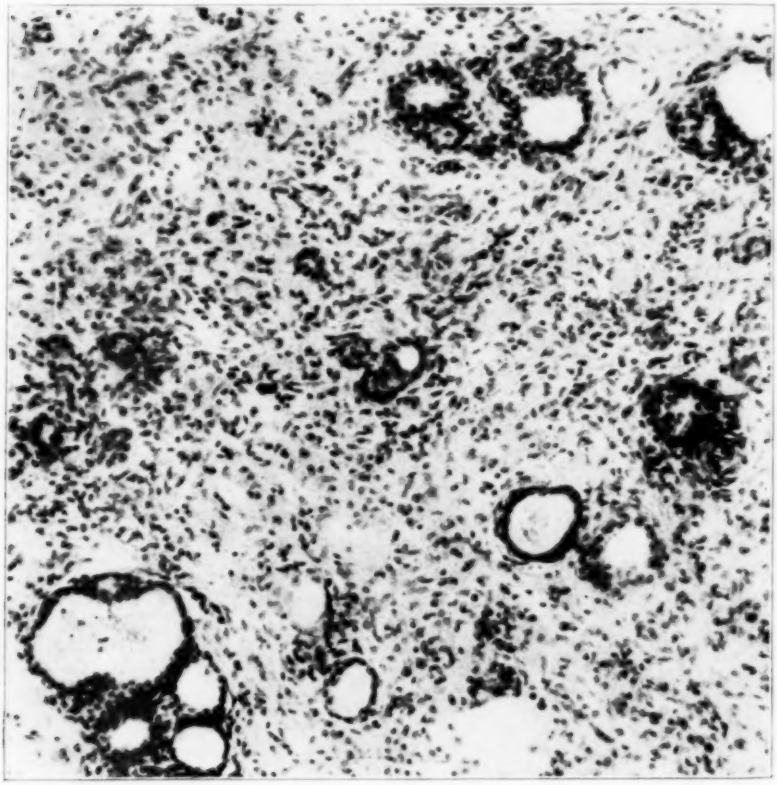


Fig. 2.—Section of thyroid removed Nov. 25, 1908, showing high-grade myxedematous atrophy. Some of the alveoli are well preserved, others are very atrophic and undeveloped. All of the alveoli are widely separated by a soft, vascular, markedly hypertrophied stroma.

appearance of the thyroid of one of these goiterous cretins in the late stages of exhaustion atrophy and the remarkable recovery as to the anatomic and chemical condition of the thyroid following the administration of a few milligrams of iodin daily over a period of two months. the puppy developed into a normal dog.

Finally, experiments were undertaken to demonstrate that the normal thyroid could be kept normal for long periods of time, even in highly goiterous districts, merely by the administration of traces of iodin. In these experiments, litters of puppies from iodized mothers were used in order to insure normal thyroids at birth. To half of each litter, 1 mg. of iodin was given by mouth once a week while the other half of each litter served as controls. These experiments were carried out in Cleveland, where practically all dogs normally have some degree

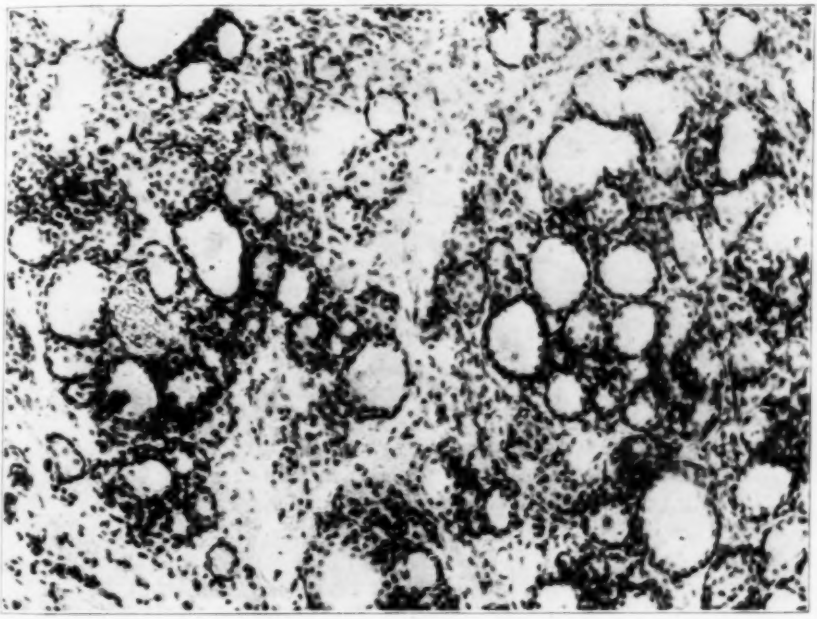
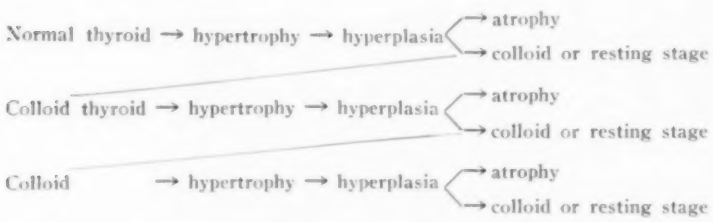


Fig. 3.—Section of the same thyroid removed Dec. 17, 1908, showing marked decrease in stroma and a corresponding relative increase and more differentiation of the alveoli.

of thyroid hyperplasia. It was found that those puppies that did not receive iodin developed thyroid hyperplasia, while the thyroids of those that received the milligram once a week remained normal, although the iodized and control puppies were kept in the same kennels and fed with the same kind of food. These experiments proved that iodin did control thyroid overgrowth, and that we had to deal with a unique physiologic fact in that a single inorganic element prevented overgrowth of the gland and controlled the functional value of its secretion.

The Anatomic Cycle in Goiter.—As already pointed out, the thyroid is a labile tissue, capable of marked hyperplasia and involution in response to variations in functional activity. On this account, a wide range and great variety of progressive, regressive, degenerative, inflammatory, atrophic and neoplastic changes may be present, many of which, as Virchow long ago pointed out, are only terminal metamorphoses and complications occurring in long-standing goiters. These secondary changes are usually present in human goiter and have caused most of the confusion and difficulties in interpretation.

The primary or basic anatomic changes in the thyroid in goiter are relatively simple. In working with large series of goiterous and nongoiterous thyroids in fish, birds, dogs, cats, sheep, cattle, pigs and rats, we have found that the cycle of essential cell changes may be reduced to a simple schema:


Normal thyroid → hypertrophy → hyperplasia → atrophy
→ colloid or resting stage
Colloid thyroid → hypertrophy → hyperplasia → atrophy
→ colloid or resting stage
Colloid → hypertrophy → hyperplasia → atrophy
→ colloid or resting stage

This cycle is the same for all animals examined, including man. The thyroid cell begins to hypertrophy when the iodin store falls below a given level, and continues this hypertrophy and hyperplasia until exhaustion atrophy or recovery supervenes. By recovery, one means the return to the colloid or resting stage, and not, as some have supposed, the disappearance of the thyroid enlargement. The colloid gland is the condition nearest to normal, both anatomically and chemically, that a gland can assume which has once been in the state of active hyperplasia, and such colloid glands are capable of all the reactions of a normal gland. They can repeat the cycle of hypertrophy, hyperplasia and involution many times, as has been shown experimentally in dogs by producing compensatory hyperplasia, by partial removal of the colloid gland, involuting this hyperplasia with iodin, again producing compensatory hyperplasia by partial removal and again involuting with iodin. We have succeeded by this method in causing the gland to repeat its cell cycle as many as seven times in the same animal. These cell charges are not specific for any clinical disease, as some have supposed, but occur in response to any stimulus for increased thyroid activity. This stimulus may be a relative or absolute lack of iodin; the increased needs of the animal for thyroid activity during infectious diseases, during pregnancy and lactation; the result of diets high in fats and protein, as shown by McCarrison.

Diseases of the Thyroid

If we omit anomalies of development, inflammations and tumors, the specific diseases in which the thyroid gland is known to play an important rôle may be divided into two groups:

1. Thyroid insufficiencies
   (*a*) Simple goiter (endemic, epidemic and sporadic)
   (*b*) Myxedema (1) Infantile (cretinism)
   (2) Adult (Gull's disease)
2. Exophthalmic goiter

These groups overlap to some extent. Myxedema may supervene in exophthalmic goiter and exophthalmic goiter may develop on the basis of simple goiter.

Thyroid Insufficiencies

From the standpoint of clinical medicine, simple goiter and myxedema are treated separately, but from the standpoint of physiology and pathology they are different stages of the same process. This fact was most clearly expressed by Morel in 1864: *"Le goitre est le première étape sur le chemin qui conduit du cretinisme."*

(*a*) *Simple Goiter.*—Simple goiter is a compensatory or work hyperplasia of the thyroid gland developing during the course of certain metabolic disturbances of unknown nature, but immediately depending on a relative or absolute deficiency of iodin. It may occur endemically or sporadically in all land and fresh water animals with the ductless thyroid. Animals living in or near the sea are relatively free from goiter. In certain parts of the world—the so-called endemic goiter districts—the incidence of goiter is greatly increased. Pittsburgh lies near the southern border of the most important district of endemic goiter in North America, the center of which is in the Great Lakes basin and the St. Lawrence River Valley.

The sudden occurrence of large numbers of goiters in man and animals has been observed—the so-called epidemics of goiter. These outbreaks have been observed in troops stationed in goiterous districts, also in fish hatcheries, on poultry farms and in dairy herds.

Etiology: The essential cause of simple goiter is unknown. The immediate cause is a relative or absolute deficiency in the iodin store of the thyroid. Goiter is, therefore, only the local sign or effect of a specific deficiency disease and may result from (1) an increase in the needs of the organism for the iodin containing hormone, as during puberty, pregnancy and lactation, during the menopause, during certain infections and intoxications, following sufficient injury to the interrenal gland (adrenal cortex) or as a result of diets consisting mainly of fat and protein; (2) interference with the absorption and utilization of the normal intake of iodin, or (3) actual deprivation of

iodin, either natural or experimental. Drinking water has been associated with the etiology from the remotest times and by all people, but we are still ignorant of the nature of the association. Foodstuffs grown in goiter districts and the water in such regions have been found to

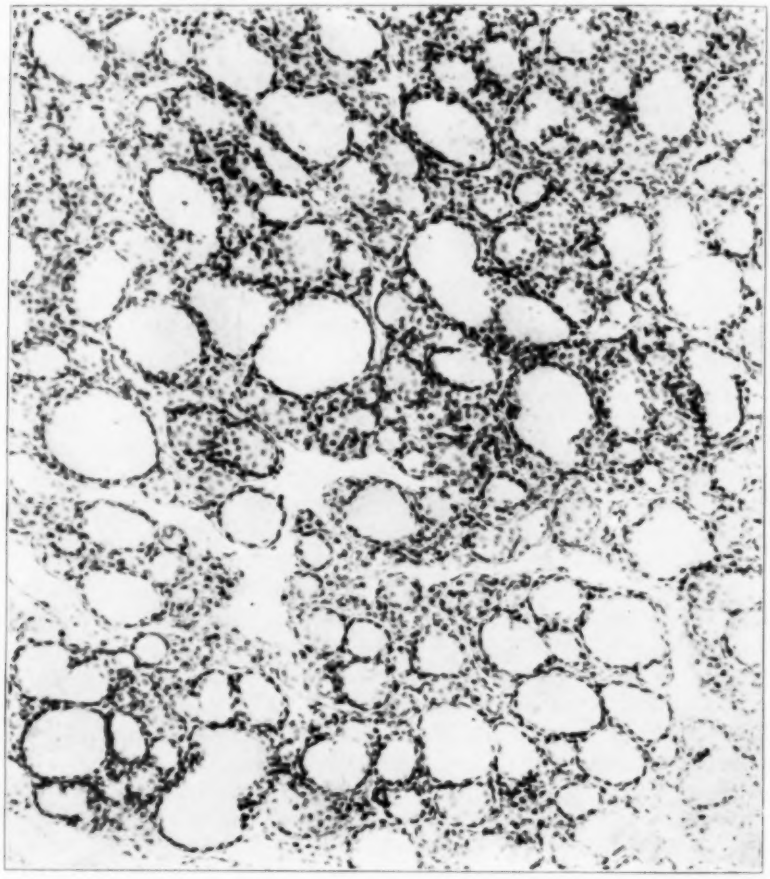


Fig. 4.—Section of the same thyroid removed Jan. 18, 1909, showing further absorption of the stroma and nearly complete differentiation of the thyroid alveoli. The epithelium and the colloid of the alveoli are normal.

contain less iodin than in nongoiterous districts. The theory that goiter is a water-born infection is without supporting evidence. That toxins of bacterial and other origin may indirectly excite the thyroid to enlargement is well known. A great variety of chemical sub-

stances has been put forward as causal agents, but none of these has been shown to have any relationship. At present the best conception of the etiology of simple goiter is that it is a compensatory or work hyperplasia immediately dependent on a relative or absolute deficiency of iodin. Whether the deficiency in iodin is primary or secondary cannot be stated at present. When one recalls that 50 mg. of iodin will maintain the thyroid in a normal state for as long as a year, and that diets rich in fat can quickly exhaust the iodin of the thyroid, it would appear that the iodin deficiency might be considered as the primary, and possibly the essential, cause. Nevertheless, we must still consider the possibility of endemic goiter being due to some chemical agent or toxin acting to divert the normal iodin intake or to increase the needs of the organism for thyroid activity.

Pathology: The first change in the thyroid in developing goiter is a marked decrease in the iodin store. When this store has fallen below 0.1 per cent., increased vascularity, cell hypertrophy and hyperplasia occur. In the lower animals, with the exception of the rat, this cellular hyperplasia is regular and uniform, while in man it is frequently irregular and nodular—struma nodosa or adenomatous goiter. These nodules or adenomas are believed to be due to different rates of growth of cell rests of different physiologic age. These nodules are an integral part of simple goiter in man. The more differentiated types are functionally active and react with iodin, while the less differentiated fetal adenomas have lost more or less completely this characteristic. Adenomas are of great importance in clinical medicine because they are so frequently the seat of hemorrhage, cyst formation, calcification and, most important of all, they form the basis of perhaps 90 per cent. of thyroid carcinomas.

Treatment: The therapy of simple goiter may be divided into two parts: (1) prevention and (2) curative treatment.

Prevention: Goiter is the easiest and simplest of all known diseases to prevent both in man and in animals. Apart from the experimental prevention mentioned earlier in this paper, iodin was first used in the prevention of goiter on a large scale in 1910, when it was demonstrated that this element added to water in concentrations not greater than 1:1,000,000 prevented the disease in brook trout. Since that time, iodin in some form has been successfully used commercially in the prevention of goiter in cattle, sheep, hogs and poultry. Iodin is effective when administered in any form or manner. This fact introduces difficulties and advantages; difficulties as to the selection of the best form and manner of administration, and advantages in that the desired result may be accomplished with certainty in a variety of ways. The ideal plan of administration of iodin for goiter prevention is still to be worked out. In private practice, from 15 to 30 c.c. of

syrup of hydriodic acid, given in from 0.5 to 1 c.c. doses daily and repeated each spring and autumn, is sufficient.

In the endemic goiter districts of America, 90 per cent. of simple goiter could be eliminated by protecting the mother and fetus during pregnancy, and the child between the ages of 10 and 17 years. The public schools offer almost ideal conditions for carrying out goiter prophylaxis in children, and maternal and fetal thyroid enlargement could be controlled by private physicians and prenatal clinics.

In a demonstration of goiter prevention in school children, Marine and Kimball administered 2 gm. of sodium iodid each spring and autumn for three years. The 2 gm. was given in 0.3 gm. doses daily. Of 2,190 pupils who took the 2 gm. as directed, only five developed thyroid enlargement, while of 2,305 who did not take the iodid, 495 developed goiter. These amounts of iodin are excessive; 0.5 gm. of sodium iodid would be as effective. In Switzerland, where the incidence of goiter is much higher, they have used iodostarin tablets containing from 1 to 5 mg. of iodin. A tablet is given once a week. If the entire population is to be protected, iodized table salt is perhaps the most practical method. Sea salt, if used exclusively, or a salt containing 0.2 per cent. iodin, if restricted to table use, would seem ample.

The mother and fetus may be protected against thyroid enlargement by the administration of 30 c.c. of syrup of hydriodic acid, or of an equivalent amount of iodin in any other available form extending over a month during the first half of pregnancy. Desiccated thyroid is theoretically a more direct prophylactic agent than iodin, but practically it is too dangerous a drug to be recommended for this purpose. The dangers from iodin administration in the doses recommended are negligible.

Curative Treatment: In long-standing goiters, no plan of medical treatment is very satisfactory. In the early developmental stages of goiter, the curative effects of iodin in the doses recommended are most striking and bring about complete relief in the majority of cases if not complicated by adenomas, hemorrhage, cyst formation or other pathologic conditions. Perhaps the most satisfactory plan of medical treatment is to administer from 2 to 4 gm. of desiccated thyroid in 0.2 gm. doses daily, and after allowing an interval of two weeks without treatment, to saturate the thyroid with iodin by giving 30 c.c. of syrup of hydriodic acid or its equivalent in iodin in from 1 to 2 c.c. doses daily. This treatment may be repeated every third or sixth month. The maximum reduction will occur in from six to twelve months. As a general rule, neither iodin nor desiccated thyroid should be given when exophthalmic goiter is suspected, although there are certain stages of this disease that are materially benefited by the administration of iodin in milligram doses.

(*b*) *Myxedema.*—This is a chronic disease due to a high-grade thyroid insufficiency and characterized by greatly reduced metabolism resulting in stunted mental and physical development if occurring during the growing period and in trophic disturbances, cachexia and mental deterioration if occurring in adults. Clinically, the disease may be arbitrarily divided into two groups, depending on whether it develops before or after puberty: (1) congenital and infantile myxedema and (2) adult myxedema or Gull's disease.

Congenital Myxedema or Cretinism: The disease occurs sporadically and endemically. The sporadic form is rare and may occur anywhere, but the endemic form is associated with endemic goiter. Goiter is the first evidence of a functional insufficiency of the thyroid, and myxedema is the end stage of the severest form of this insufficiency. Many observers believe that cretinism is a more complex nutritional disturbance than can be accounted for on the basis of thyroid insufficiency. This belief is based on the facts that many other conditions—dwarfism, rickets and Mongolian idiocy—have in the past been confused with cretinism and that postnatal treatment with desiccated thyroid is usually only partially successful, while in the myxedema of adults, treatment with desiccated thyroid is highly successful. The postnatal therapeutic test is not a physiologic test for the reason that the greatest effects of thyroid insufficiency occur during fetal and early postnatal life. A more appropriate test would be to administer desiccated thyroid or iodin to the mother during pregnancy. The question is raised because of the ease with which congenital myxedema in animals may be controlled by the administration of iodin or desiccated thyroid during pregnancy or during the first weeks after birth.

All the experimental work indicates that the primary and essential lesions in cretinism may be directly ascribed to thyroid insufficiency. A loss of thyroid function sufficient to cause recognizable myxedema may have varied etiology. Injury or destruction of the gland by infection or trauma, congenital absence or smallness of the thyroid anlage, or atrophy of unknown nature are the most common causes of sporadic infantile myxedema, while endemic goiter is the most important additional factor in endemic myxedema.

Pathologic Physiology: The essential physiologic fault is a deficiency of the iodin-containing hormone. In surviving cretins the loss is rarely complete, as in the severest form both animals and man die soon after birth. Although cretinism may occur in the first generation of goiterous parents, it is usually the summation of several generations of goiterous progenitors.

Treatment: Prevention offers the only certain means of controlling the disease both in man and animals. The postnatal treatment is only partially successful because too much damage has been done before

treatment can be instituted. Remarkable cures may be obtained in cretin animals when treatment can be started shortly after birth. Since all the available evidence indicates that endemic cretinism is due to the same physiologic fault as endemic goiter, and since congenital myxedema may be readily controlled in animals by the administration of iodin to the mother during pregnancy, I believe that the elimination of endemic cretinism is as simple as the elimination of endemic goiter, and can be accomplished by the same means. To this end it is necessary to see that the mother obtains 2 to 5 mg. of iodin weekly in some available form during pregnancy and that this be continued from time to time during the growing period of the child. Just as in the prevention of endemic goiter, the most practical means of prevention will probably be the state-wide use of salt containing from 1 to 2 mg. of iodin per gram.

Myxedema of Adults (Gull's Disease). This is the best understood effect of a pathologic decrease in thyroid function, because it is not complicated by the ill-understood and intricate chemical processes of growth and development. Spontaneous and operative or experimental myxedema are essentially identical. The first experimental myxedemas, reported in 1882 and 1883, were produced in man by the Reverdin brothers and by Kocher by the removal of goiters. Spontaneous myxedema is from six to eight times more common in women than in men, and exophthalmic goiter is the most important antecedent. The disease, as pointed out by Gull, is usually associated wtih exhaustion atrophy of the thyroid, but occasionally thyroid enlargement may be present. In endemic myxedema, thyroid enlargement is the rule. As regards treatment, in the rare instances in which there is abundant active thyroid, iodin is as efficacious as desiccated thyroid, just as in congenital myxedema. In all other cases, the iodin-containing hormone must be supplied—best in the form of desiccated thyroid. The treatment of myxedema by thyroid, discovered by Murray in 1891, is one of the triumphs of applied physiology.

EXOPHTHALMIC GOITER

While studies in pathology and physiology have as yet contributed very little toward clearing up the nature of this obscure disease, they have indicated that the most suggestive lead lies in the field of the interrelations of glands of internal secretion. Exophthalmic goiter may be defined as the manifestation of a disturbance of the regulatory control and functional interactions of organ activities, characterized by increased metabolism of thyroid origin, asthenia and tachycardia. The thyroid plays an important rôle in the clinical manifestations of the disease, but we must look beyond this gland for the essential and primary lesions. So, also there is evidence that the thymus, liver, sex

glands, suprarenal (adrenal medulla) and interrenal glands (adrenal cortex) are also involved in an important way.*

It was in the hope of finding additional facts regarding thyroid interrelations, and possibly some new data relative to exophthalmic goiter, that I undertook an investigation of the thyroid sex-gland interrelations. The thyroid sex-gland interrelationship is perhaps one of the longest known and most striking examples of interrelations of glands with internal secretion. Thyroid enlargement is intimately associated with the cyclic activities of the sex glands, and it occurred to us that since the adrenal cortex is in many ways closely related to the sex glands, further data on the sex-gland-thyroid interrelationship might be obtained by studying the effects of cortical injury on thyroid function. I have used heat production as the best available method for measuring variations in thyroid activity. Golyakowski, in 1899, first observed the increased heat production which follows severe but sublethal injury to the adrenals in the dog.

In collaboration with Drs. Baumann and Scott, I have studied the heat production in a large series of rabbits and cats following adrenal injury. In rabbits we have produced adrenal insufficiency by removal of the glands and by freezing the cortex after mobilization with as little injury to the blood and nerve supply as possible. In cats, we have in addition utilized the method of vein ligation. The reactions as to heat production following these forms of injuring the adrenal function may be divided into three groups: (1) those that survive indefinitely with no appreciable alterations in heat production; (2) those that show an increase in heat production, and (3) those that show a fall in heat production. Of thirty-three rabbits in which both adrenals were removed, twenty-seven, or 82 per cent., showed a rise in heat production varying from 10 to 63 per cent. The rise is absolute and usually begins in from three to six days after removal or injury of the adrenals and lasts from a few days to several months. Sometimes in rabbits, and frequently in cats, the rise in heat production is preceded by a fall lasting two or three days.

Infection, trauma and nerve injury, it is believed, may be eliminated as important factors in this increased heat production. The simplest explanation for the increased heat production with the facts at present available, is that it is in part due to increased thyroid activity brought about by the removal of the regulatory and inhibitory influence normally exercised by the adrenals, and that it is dependent on cortical rather than on medullary function. In order to determine whether the thyroid

* On account of the dual nature of the suprarenal gland the terminology of comparative anatomy has been adopted, namely, "adrenal gland" includes both the medulla and cortex; "suprarenal gland" includes only the medulla or chromophil tissue and the "interrenal gland" includes only cortical tissue.

was a factor in the increased heat production, fifteen experiments were carried out: After control heat production measurements had been made over a period of from two to three weeks, the thyroid glands were removed and the metabolism allowed to fall to its lowest level, usually in about three weeks, and then the adrenals were removed either in one or two sittings and heat production measurements continued until the animal died or until further observations seemed unnecessary. In only two instances after adrenalectomy were there significant rises in heat production above the level obtaining after thyroidectomy, but in no instance did the heat production rise to the normal level.

The striking feature of these experiments is the absence of a significant rise in thirteen of fifteen rabbits in which adrenalectomy was performed after thyroidectomy, in comparison with a rise of more than 10 per cent. in twenty-seven of thirty-three rabbits with intact thyroids, in which the adrenals were removed. Further, there is evidence that the iodin store in the thyroid is markedly reduced during the period of increased heat production following injury to the adrenals, and, in addition, we have been able to cause secondary rises in heat production after thyroid exhaustion by the adminisration of a few milligrams of iodin. These facts, we believe, establish another thyroid-adrenal interrelationship which, with our present knowledge, seems to depend on an antagonistic action of the thyroid and interrenal gland (adrenal cortex). The fact that increased heat production occurs after removal of most of the chromophil tissue, indicates that epinephrin has very little to do with it. It is possible that, if increased epinephrin discharge could be combined with interrenal insufficiency, a much greater rise in heat production could be brought about. It should be pointed out that while the thyroid-interrenal gland interrelationship appears to be an important one, it is only one of many functions in which the interrenal gland is directly or indirectly concerned.

In this connection, it is appropriate to refer to some measurements of heat production in infants during the normal involution of the adrenal gland, which begins during the second week of extra-uterine life. This involution is a remarkable destruction of the two inner layers of the cortex. It begins as a hemorrhagic infiltration, going on to necrosis and finally to absorption of these layers, with a folding and collapse of the glomerular zone on to the medulla. While the physiologic significance of this normal destruction of the cortex in human infants' adrenals is unknown, it occurred to us that it might be in effect a naturally occurring cortical injury bringing about an alteration in heat production similar to that found in animals following experimental sublethal destruction of the cortex. Lowe and Cipra and I studied the heat production in ten normal infants every second or

third day from birth to the thirty-fifth day of life. A sharp rise in heat production was observed during the second week of extra-uterine life, coinciding with the onset of the cortical destruction. Our figures were as given in the table.

Rise in Heat Production After Birth

	Calories per kg. per hour
From 1 to 7 days	1.88
From 8 to 14 days	2.14
From 15 to 21 days	2.15
From 22 to 28 days	2.30
From 29 to 34 days	2.34

The rise during the second week was much greater than the combined rise during the next three weeks of observation. A rise in heat production follows both the normally occurring and the experimentally produced injuries to the interrenal gland, provided the thyroid gland is intact, but it does not occur in animals when the thyroid gland has been previously removed. If the interrenal gland directly or indirectly exercises a restraining or regulatory control over the thyroid gland, it may be found to have an important relation to the etiology of exophthalmic goiter. In studying the clinical manifestations of chronic sublethal interrenal insufficiency in cats and rabbits, one is impressed by the points of similarity between it and some of the outstanding features of exophthalmic goiter. The most prominent single feature in each is a significant increase in heat production. Each condition has a phase of increased fatigability, asthenia and exhaustion. In both conditions, there is evidence of myocardial injury. Diarrhea, increased or decreased appetite, nutritional and weight changes, are present in both. A rapid loss of iodin associated with thyroid hypertrophy is also present in each. Finally, that rather rare form of exophthalmic goiter, running a fatal course in a few weeks, with marked asthenia, tachycardia, hyperthermia and coma, bears a striking resemblance to the effect produced by experimental interrenal insufficiencies terminating fatally in one or two weeks.

ELECTIVE LOCALIZATION IN THE EYE OF BACTERIA FROM INFECTED TEETH *

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An etiologic relationship between chronic foci of infection and systemic disease is accepted by most clinicians. The cure or marked improvement in some systemic disorder which may follow the removal of a septic focus seems conclusive proof of a causal relation. The clinical manifestations of focal infection depend primarily on the site of localization of the bacteria which are fed into the blood stream. The extent of clumping of the organism, the nature of the blood supply, the food supply and local tissue resistance must play important parts in determining the localization and resulting infection.

Rosenow [1] has emphasized also the individual variation in bacteria and has advanced the theory that bacteria have a specific tendency to localize in certain tissues of the body, dependent on some peculiar inherent property. The theory is a most attractive one and has evoked a great deal of discussion. If it is true that bacteria have peculiar localizing or infecting powers, many obscure phenomena of disease are explained. The theory concerns especially the streptococci commonly associated with chronic disease of bacterial origin. Rosenow has demonstrated that such streptococci freshly isolated from infected tissues and from foci of infection in patients suffering from rheumatic fever,[2] erythema nodosum,[3] ulcer of the stomach, cholecystitis, herpes zoster, myositis,[4] appendicitis and epidemic parotitis,[5] and acute poliomyelitis,[6] tend to reproduce in animals the lesion from which the patient suffered. Bumpus and Meisser,[7] Meisser and Gardner,[8] Hardt [9]

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1. Rosenow, E. C.: Elective Localization of Streptococci, J. A. M. A. **65**: 1687 (Nov. 13) 1915.

2. Rosenow, E. C.: The Etiology of Acute Rheumatism, Articular and Muscular, J. Infect. Dis. **14**:61, 1915.

3. Rosenow, E. C.: The Etiology and Experimental Production of Erythema Nodosum, J. Infect. Dis. **14**:367, 1915.

4. Rosenow, E. C.: Studies on Elective Localization—Focal Infection with Special Reference to Oral Sepsis, J. Dent. Res. **1**:205, 1919.

5. Rosenow, E. C., and Dunlap, Stella I.: An Epidemic of Appendicitis and Parotitis Probably Due to Streptococci Contained in Dairy Products, J. Infect. Dis. **18**:383, 1916.

6. Rosenow, E. C.; Towne, E. B., and V. Hess, C. L.: The Elective Localization of Streptococci from Epidemic Poliomyelitis, J. Infect. Dis. **21**:313, 1918.

7. Bumpus, H. C., and Meisser, J. G.: Foci of Infection in Cases of Pyelonphritis, J. A. M. A. **77**:1475 (Nov. 5) 1921.

8. Meisser, J. G., and Gardner, B. S.: Elective Localization of Bacteria Isolated from Infected Teeth, J. Nat. Dent. Assn. **9**:578, 1922.

9. Hardt, L. L. J.: The Secretion of Gastric Juice in Cases of Gastric and Duodenal Ulcer, Am. J. Physiol. **40**:314, 1916.

and others working with or under the direction of Rosenow have reported similar results. The greater number of workers have, however, failed to obtain evidence of an elective localization. Thus Moody [10] found no evidence of a tendency to specific localization in the injection of bacteria from chronic dental foci. Henrici,[11] in studying the specificity of streptococci, could demonstrate no tendency of the organism to reproduce the disease from which the patient suffered. Meyer [12] suspects the selective action of bacteria, and considers that it is the tissues of the animal which determine the local lesion.

Few of those who have attempted to verify Rosenow's work have given the proper consideration to certain fundamental technical details. The bacteria employed in animal inoculations have often been subcultivated aerobically. Rosenow has emphasized that the bacteria concerned in chronic foci are very sensitive to oxygen, and that the property on which elective localization depends tends to disappear promptly on aerobic cultivation. To demonstrate an elective localizing power the culture medium must be favorable with regard to oxygen tension, and the animal inoculations must be made with freshly isolated cultures. The necessity for providing the proper oxygen tension in the culture medium cannot be emphasized too strongly. There is much to suggest that an adaptation to a certain oxygen tension is largely the determining factor in elective localization. It has been well stated [13] that "a focus is of importance not only as affording an entrance way for bacteria but also as a place where varying affinities may be acquired."

It is important to decide, if possible, whether bacteria do have a selective affinity. Certainly the best experimental proof we have of the etiologic relationship of a focus of infection to a certain lesion is the reproduction of the lesion in animals by the injections of bacteria isolated from a focus in the patient. It is still better proof of an etiologic relation if it is shown that the reproduction of the lesion is dependent on the specific tendency of the bacteria to produce the lesion which the organism causing the patient's infection is evidently producing.

Certain considerations in a study of elective localization should be emphasized. Some lesions are exceedingly easy to produce in animals. Thus joint involvement is commonly found after the intravenous injec-

10. Moody, A. M.: Lesions in Rabbits Produced by Streptococci from Chronic Alveolar Abscesses, J. Infect. Dis. **19**:515, 1916.

11. Henrici, A. T.: The Specificity of Streptococci, J. Infect. Dis. **19**:572, 1916.

12. Meyer, K. F.: Discussion in Symposium on Removal or Retention of Teeth, J. Nat. Dent. Assn. **7**:175, 1920.

13. Rosenow, E. C.: Relation of Dental Infection to Systemic Disease, Dental Cosmos **59**:485, 1917.

tion of many different types of bacteria. The production of arthritis in an animal with the bacteria isolated from an infection in a patient suffering from arthritis, in a single instance, is little proof of a causal relation and still less of elective localization. The only data of value are those showing that the bacteria from a large group of persons with arthritis produce arthritis in a much higher percentage of animals than those from a similar number of persons not suffering from arthritis.

The lesions which are especially desirable for a study of elective localization are those which occur rarely on routine intravenous injection. We have recently been observing the lesions produced in animals by the intravenous injection of bacteria isolated from chronic periapical dental infection. During this time we have had the opportunity of noting the lesions produced by streptococci isolated from dental areas of infection in a group of patients suffering from infections of the eye. The results seem to offer some data of value in determining the truth of the theory of elective localization and the relationship of the infection to the diseased process.

Eye infection occurring in animals after intravenous injection may be a part of the widespread lesions of a septicemia, associated with an infection of the central nervous system, or a specific localization in the eye. Involvement of the eye is seen only in a small proportion of animals on routine injection. Rosenow [13] found eye infections in thirty-two of 833 animals injected with cultures from varying sources. Moody [10] obtained eye infections in 1.7 per cent. of 178 animals injected with bacteria from dental foci. The accessibility of lesions of the eye to direct observation and ophthalmoscopic examination is also a great advantage in such an experimental study.

A close clinical relationship between oral sepsis and infections of the uveal tract has long been recognized. Black,[14] in summarizing the literature concerning ocular disease resulting from dental lesions, cites clinical reports bearing on this relation which were published as early as 1842. Butler,[15] in a study of 100 cases of infection of the uveal tract, decided that 12 per cent. were definitely due to oral sepsis. He considered that the etiology of 41 per cent. was doubtful, but concluded that probably a large part of these originated in oral sepsis. B. T. Lang [16] classified 71 out of 176 cases of eye infection as due to septic foci about the teeth. William Lang [17] thought that pyorrhea

14. Black, A. D.: Ocular Disorders Resulting from Dental Lesions, Ophth. Rec. **24**:1915, 1915.

15. Butler, T. H.: Etiology of Iritis, Brit. M. J. **1**:804 (April 8) 1911.

16. Lang, B. T.: Influence of Septic Infection in the Causation of Eye Disease, Brit. M. J., Feb. 22, 1913.

17. Lang, William: Influence of Chronic Sepsis on Eye Disease, Lancet, May 17, 1913, p. 1368.

was responsible for 139 of 215 cases reported by him. De Schweinitz [18] aptly sums up the question in the statement that there is "no better established etiological relationship than that between septic foci in dental areas and certain diseases of the eye, especially those of the uveal tract." Such conclusions are based largely on the clinical improvement noted after the eradication of foci of infection.

There is little experimental proof, however, of a relation between focal infection and eye disorders. Irons, Brown, and Nadler [19] studied a streptococcus isolated from the infected tissues of a patient suffering from dacrocystitis and iritis. They found that a large percentage of rabbits developed eye lesions when injected intravenously with the freshly isolated culture. The ability to produce specific lesions was lost on subculture and on passage. The loss of specific tendency to localize in the eye was not accompanied by any demonstrable decrease in virulence for rabbits. Rosenow [20] has reported cases of eye infection from a dental pulpitis with the reproduction of the lesion in animals. Meisser and Gardner [5] have reported a similar case.

METHODS

In making the bacteriologic studies of tooth infections I have followed closely the methods of Rosenow.[4] All cultures have been made in glucose brain broth and glucose brain agar. The mediums are prepared according to Rosenow's directions:

Glucose Brain Broth: dehydrated bacto nutrient broth, 8 gm.; sodium chlorid, 8 gm.; dextrose, chemically pure, 2 gm.; Andrade indicator, 10 c.c., and distilled water, 1,000 c.c. The broth and salt are dissolved by heating. After cooling, the indicator and dextrose are added. The medium is tubed in 6 by three-fourths inch test tubes so that the depth is at least 3½ by 4 inches. Three pieces of calf brain, about 1 c.mm. square, and two or three pieces of crushed marble are added to each tube. The tubes are then sterilized for twenty minutes in the autoclave at 20 pounds' (9.07 kg.) pressure.

Glocose Brain Agar: The agar medium is made by adding 7 gm. of powdered agar to 1 liter of the glucose brain broth prepared as indicated above. The calf brain and marble are then added, and the medium is sterilized.

The brain substance renders the bottom of the medium anaerobic; the top is aerobic, so that every degree of oxygen tension between these two points is provided. The nutritive qualities of these mediums are especially favorable for the growth of the organisms encountered in infections about the teeth. The agar medium we have found especially valuable in showing the relative number of bacteria present in the material inoculated. It will barely solidify but is hard enough to hold colonies discrete without restraining growth. The appearance of a brain agar tube is shown in Figure 1.

18. De Schweinitz, George E.: Dental Sepsis in Its Relation to Ocular Disorders, Dental Cosmos **42**:565, 1920.

19. Irons, E. E.; Brown, E. V. L., and Nadler, W. H.: The Localization of Streptococci in the Eye. A Study of Experimental Iridocyclitis in Rabbits, J. Infect. Dis. **18**:315, 1916.

20. Rosenow, E. C.: Focal Infection as a Cause of Iritis, Med. Clin. N. America **5**:573, 1921.

In making cultures of tooth infections the greatest care is necessary to avoid surface contamination. We have found that sterile cultures can be quite uniformly obtained from the tips of anterior vital teeth by the procedure which we have employed. It is apparent that unless sterile cultures can be obtained from noninfected vital teeth, cultures of pulpless teeth are of little value. We have utilized the following technic: Before extraction the teeth are thoroughly scrubbed with gauze, after which the field of operation is painted with tincture of iodin. Care is taken that the iodin penetrates well into the space between the gum margin and tooth, and between the teeth. The iodin is removed with alcohol and the area of operation walled off with sterile gauze.

The tip of the extracted tooth is cut off with sterile forceps directly into a test tube containing a few cubic centimeters of sterile salt solution and a small amount of sharp sand. The tubes are well shaken to macerate the tissue on the tip of the tooth as completely as possible. The mediums are inoculated by

Fig. 1.—Original glucose brain agar culture tube from the tip of tooth indicated by arrow in Fig. 4.

pouring the salt solution containing the suspended tissue into a tube of agar which had been heated and cooled to 40 C. The tube is quickly inverted once and allowed to harden. The small amount of salt solution remaining in the tube is poured into a tube of glucose brain broth. The inoculated tubes are incubated at 37 C. for from twenty-four to forty-eight hours. A smear is made from the broth culture and stained by Gram's stain. A transplant of the broth culture is made to a blood agar plate. Subcultures are made of streptococci from the blood agar to lactose, mannite and salicin fermentation tubes. According to the appearance of the colonies on blood agar and the fermentation reactions, the streptococci are classified by Holman's table.[21]

Rabbits have been injected intravenously with the broth culture as soon as a good growth was obtained. This was never more, and usually less, than

21. Holman, W. L.: J. Med. Res. **34**:377, 1916.

twenty-four hours. When cultures were taken from several teeth from one patient, the several broth cultures were often mixed before injection. The rabbits varied somewhat in size but averaged about 1,500 gm. Each animal was given 5 c.c. of the broth suspension.

The animals have been watched carefully for eye lesions. Usually necropsy was performed on one animal from each culture three days after the injection, and on the second six days after injection. Occasionally animals have been kept for longer periods for observation. One animal has been observed for nine months. At necropsy the animals were carefully examined for lesions. No lesions were considered as present unless plainly visible to the naked eye. Microscopic sections have been made of many of the tissues. Cultures have often been made of the organs at necropsy, but not in a routine manner.

The patients studied have all suffered from eye infections which were considered as blood-borne and possible manifestations of focal infection. Patients with a positive Wassermann test have all been excluded except one (Case 5), which was included before the Wassermann report was received. A complete physical examination was made in all cases but one. The tonsils had not been removed from some patients, and could not be excluded as an additional factor. No apparent foci except the teeth and tonsils were found.

EXPERIMENTAL OBSERVATIONS

Positive cultures were obtained from the root tip or pulp of one or more teeth of fifteen patients suffering from metastatic eye infections. Staphylococci and streptococci were the only organisms recovered. Streptococci were found almost constantly as the predominant organism. Staphylococci were occasionally observed in pure culture but were usually present only in small numbers in association with streptococci. No relation has been found between the type (Holman) of organism and the pathogenicity.

Sixty-six rabbits have been injected intravenously with the bacteria isolated (Group 1). At least two rabbits were injected with the single culture or the mixed cultures from a patient. Two animals were used for the culture from each tooth found infected in several patients. Forty-five, or 68.2 per cent., of the sixty-six rabbits developed eye lesions. The positive findings include one or more rabbits from fourteen patients. The one patient whose cultures produced no syphilitic lesions was found later to have a positive Wassermann test.

As a control on these results we have the result of the inoculation of 169 rabbits by the same uniform technic with the cultures from the teeth of patients who were suffering from no systemic disease or from systemic disease other than infection of the eye (Group 2). Of this group, twenty-five, or 14.8 per cent., had lesions in the eye; twelve, or nearly 50 per cent., of these were associated with meningitis; the majority of the remaining thirteen were a part of an evident septicemia with generalized lesions. Only six, or 13 per cent., of the lesions in Group 1 were associated with meningitis, and few animals showed evidences of a septicemia.

The percentage of lesions in the principal organs affected in the two groups are shown in the table. The incidence of joint involvement is about the same in the two groups. The muscle, kidney, heart, brain, stomach and duodenum showed a smaller percentage of lesions in Group 1 than in Group 2. Numerous animals in Group 1 showed no lesions except those of the eye. The fact that organs other than those involved in the patient are affected in the animal is taken by some as evidence against the theory of selective localization. Careful examination of patients will demonstrate, however, that few suffering from focal infection show only one manifestation of metastatic localization. The presenting lesion is usually simply the predominant one.

The most common anatomic lesion was an iritis or iridocyclitis. Some animals showed multiple hemorrhages in the iris, limbus or sclera, cloudy fluid in the anterior chamber, cloudy cornea and hyalitis. Drawings from life of typical lesions are shown in Figure 2. Pericorneal

Localization of Bacteria Isolated from Infected Teeth *

	Number of	Percentage of Animals Showing Lesions in								
Group	Animals	Joint	Muscle	Kidney	Endocardium	Myocardium	Brain	Eye	Stomach and Duodenum	Gallbladder
1	66	65.2	22.7	39.4	10.6	4.5	10.6	68.2	1.5	0.0
2	169	66.7	35.5	48.5	13.0	10.6	12.4	14.8	10.1	0.6

* Group 1 consists of animals injected with bacteria isolated from teeth of patients suffering from metastatic eye infection. Group 2 consists of animals injected with bacteria isolated from teeth of patients suffering from no systemic disease or from systemic disease other than eye infection.

injection often developed a few hours after the inoculation. In some animals the injection was progressive, in others it disappeared, only to reappear at a later date with an evident infection.

Histologic examination of the eyes showed injection of vessels (Fig. 9), or hemorrhage in the iris and ciliary body in some specimens. Others showed the diffuse inflammation of a panophthalmitis, including the extra-ocular muscles. Still others showed a marked cellular infiltration of the choroid (Fig. 11). One showed only an infiltration of cells in the vitreous humor (Fig. 12). Typical histologic findings are show in Figures 9, 10, 11 and 12.

Cultures were not made according to routine from all the eyes affected, as the specimens were preserved for histologic examination. Numerous cultures have been made, however, from the iris, and aqueous or vitreous humor. Organisms were recovered from all eyes from which cultures were taken during the course of an active infection. In one instance, the organism was carried through three series of animals.

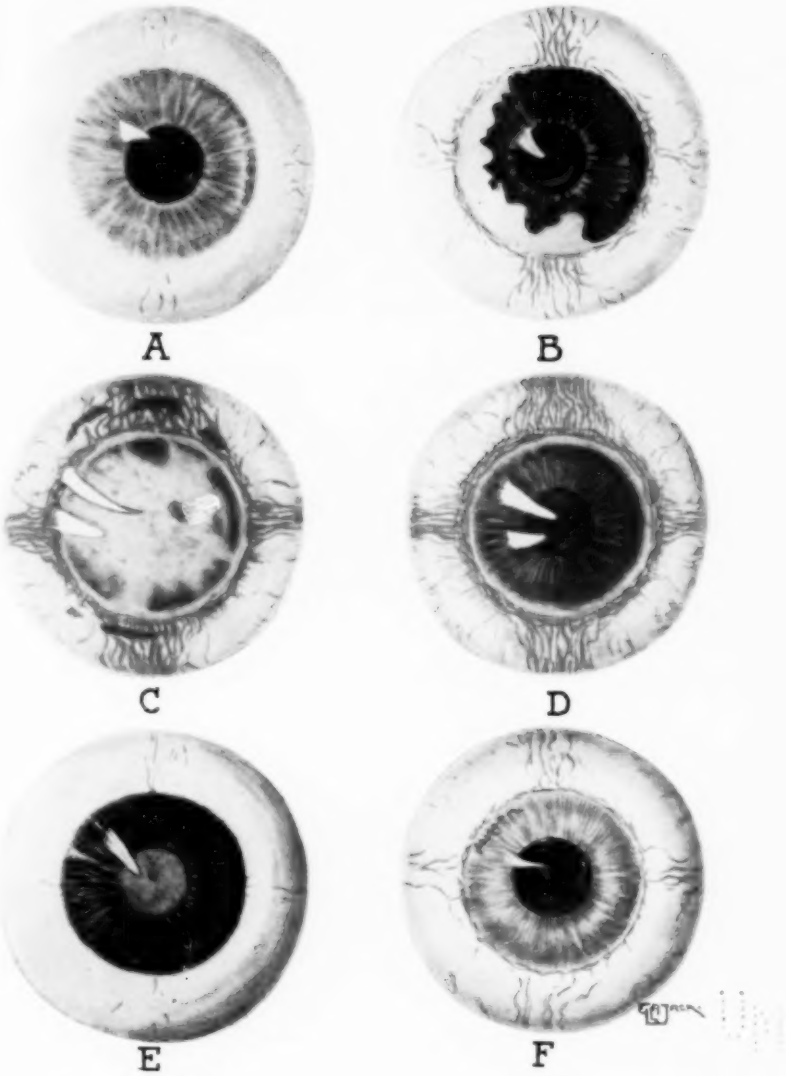

Fig. 2.—*a* represents the normal eye of an albino rabbit. *b*, the left eye of Rabbit 4, forty-eight hours after the intravenous injection of a culture from the root tip (Fig. 4) in a case of recurrent hyalitis (Case 1). Note the exudate in the anterior chamber and the circumcorneal injection. *c*, eye of Rabbit 87 injected with the cultures of root tips in a case of iritis, and episcleritis (Case 10). Note the pericorneal injection, hemorrhages in iris and sclera and exudate in anterior chamber. *d*, eye of Rabbit 95 injected with the mixed cultures of the root tips of the upper incisor teeth (Fig. 5), in a case of recurrent iritis (Case 8). A photomicrograph of the iris and ciliary body of this eye is shown in Figure 10. *e*, right eye of Rabbit 12 eight days after the intravenous injection of the attenuated culture from the root tip (Fig 4) in a case of recurrent hyalitis (Case 1). Note the absence of light reflex due to an opacity of the vitreous humor. A photomicrograph of the vitreous of this eye is shown in Figure 11. *f*, eye of Rabbit 43, six months after the injection of cultures from the root tips in a case of iridocyclitis following the removal of a congenital cataract (Case 4). This animal had recurring attacks of iritis.

COMMENT

The fact that 68.2 per cent. of the animals injected with bacteria isolated from tooth infection in patients suffering from metastatic eye infection developed eye infections, while only 14.8 per cent. of the animals inoculated with cultures from other sources showed similar lesions, could hardly be explained otherwise than by granting a selective action on the part of the bacteria. The findings thus offered confirmatory evidence of the validity of Rosenow's theory of elective localization. Our results have an added interest in that they demonstrate again experimentally the well recognized clinical relation of dental infection to ocular disease.

In a number of instances we have been able to produce specific eye lesions with bacteria isolated from the tips of teeth which seemingly showed no evidence of infection in the radiograph. We have found repeatedly that large numbers of bacteria may be grown from a root tip around which there is not enough destruction of bone to be evident in the radiograph. This needs to be emphasized because often infection around a pulpless tooth is ruled out simply because the radiograph does not show bone absorption. Such teeth are often allowed to remain in the jaw even in the presence of serious metastatic systemic disease in which the eradication of all possible foci is urgently indicated.

Some of the case histories reported below illustrate a number of the problems encountered in the management of chronic peridental infection. Case 8 is of special interest. The complete radiographs are shown in Figure 5. The only tooth around which there is evident bone destruction is indicated by an arrow. On culture this showed a large number of colonies of a streptococcus which produced no eye lesions in rabbits. An animal inoculated with the mixed cultures from the upper incisor teeth developed the eye lesion shown in Figure *2 d*. The patient stated that the worst attack of iritis which he had suffered occurred while the dental restorative work on the upper incisors was being done.

One patient (Case 12) had no pulpless teeth. A molar tooth (Fig. 6) which had a large filling was removed, largely because there was a pocket around it which could not be cleaned up well otherwise. The tooth had responded normally to tests for vitality, but on opening the pulp chamber under sterile precautions, the pulp was found to be swollen and hyperemic. From the pulp a pure culture of a green-producing streptococcus was obtained. The eye of a rabbit injected with the mixed cultures from the root tip and pulp is shown in Figure 7. On further questioning there seemed to be an evident connection between the infection of this tooth and the patient's first attack of iritis. Two patients (Cases 4 and 10) developed infections of the eye subsequent to an operation on the eye, such as the removal of a

cataract. Here the localized diminished resistance must also have been a factor in the localization of the bacteria. Two patients had iritis with arthritis. Another had attacks of iritis with chronic glaucoma. The case reports and protocols of animal experiments in the individual cases are reported in detail below.

SUMMARY

A study of the eye lesions produced in rabbits by the intravenous injection of streptococci and staphylococci isolated from chronic dental infection is reported.

All cultures have been made in Rosenow's glucose brain mediums to afford the proper nutritive material and the optimum oxygen tension.

The animals were inoculated with freshly isolated cultures; usually the injection was made within twenty-four hours after the extraction of the tooth.

Sixty-eight and two tenths per cent. of sixty-six rabbits inoculated with the cultures obtained from fifteen patients suffering from metastatic eye infection developed lesions of the eye.

Fourteen and eight tenths per cent. of 169 rabbits inoculated with cultures from patients other than those suffering from eye disease developed lesions of the eye.

The much higher percentage of animals showing lesions in the eye when inoculated with bacteria from patients suffering from ocular diseases indicates some selective affinity of the bacteria for tissues of the eye.

The results offer proof of the etiologic relation of infection in dental areas to diseases of the eye.

Teeth which are negative in the radiograph may bear as important an etiologic relation to disease as those which show evident infection.

CASE REPORTS AND PROTOCOLS OF ANIMAL EXPERIMENTS

CASE 1.—*Recurrent hyalitis.* L. P., a steamfitter, aged 25, was first seen, June 25, 1920. He complained of seeing something flying around in front of the right eye. This was first noticed about three weeks before following an attack of influenza. It was gradually becoming worse.

The fundus was seen with difficulty, but no hemorrhages were present. Many fine dustlike opacities and some larger ones were floating freely in the vitreous, also shreds of hyaloid tissue, to which were attached numerous dustlike opacities. There was no opacity of any kind to be found in the aqueous or on the back of the cornea and no inflammation was apparent. The vision in the right eye was 20/100.

Under treatment the vision became better, 20/50, and at one time 20/40. Between June, 1920, and February, 1922, the patient had had four light attacks and one severe one which left the eye almost without a reflex. These exacerbations did not come on suddenly as they would have if they had been recurrent hemorrhages. From the time of his first visit the patient was urged to have all his pulpless teeth extracted, but several were not removed.

A general physical examination on Feb. 24, 1922, was negative. The tonsils had been removed. Blood examination revealed: red cells, 4,632,000; hemoglobin, 90 per cent.; white cells, 7,400. The differential count was polymorphonuclear neutrophils, 55.5 per cent.; polymorphonuclear eosinophils, 4.5 per cent.; polymorphonuclear basophils, 2 per cent.; small mononuclears, 25.5 per cent.; large mononuclears and transitionals, 12.5 per cent. The urine showed no abnormality, and the Wassermann test was negative. A roentgenogram of the teeth showed that the upper left cuspid (Fig. 4), and the lower left second bicuspid were pulpless with poor canal filling and some bone absorption at the root tip. The lower left lateral incisor was a peg tooth, the root was poorly filled, and there was a large alveolar abscess. The three pulpless teeth were extracted. The brain agar cultures showed no growth from the lower left lateral incisor, and only a few colonies from the lower left second bicuspid. The culture of the upper left cuspid showed an infinity of colonies of a nonhemolytic streptococcus (Figs. 1 and 3). March 1, 1922, Rabbits 3 and 4 were injected with the broth culture from the upper left cuspid. Rabbit 3 developed numerous patches of choroidoretinitis and died three weeks later. The necropsy findings were ascites and very large white kidneys. Rabbit 4 developed exudate in the

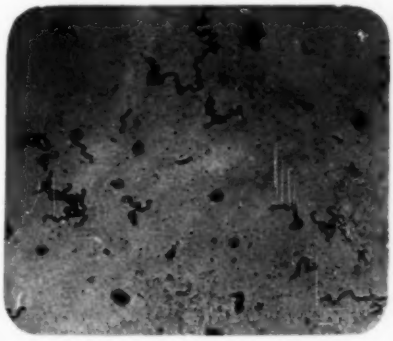

Fig. 3.—Photomicrograph of streptococcus from culture tube in Figure 1.

anterior chamber and corneal opacities of both eyes twenty-four hours after inoculation. The following day the eyeballs were extremely red. The right iris was discolored all the way around and the left partly around (Fig. 2 *b*) with a milky gray exudate. There were grayish deposits on the cornea. The animal was killed. Necropsy was negative except for the eye findings. The streptococcus was recovered by smear and culture from both eyes. On March 5, Rabbits 5 and 6 were inoculated with streptococcus recovered from the left eye of Rabbit 4. Rabbit 5 developed circumcorneal injection and a choroidoretinitis and died thirteen days later. Necropsy showed only kidney abscesses. Rabbit 6 developed a marked injection of both eyes and died within twenty-four hours. A short chain streptococcus was recovered from the eye. Two rabbits injected with this culture died in a few hours without showing any localized lesions. Rabbits 7 and 8 injected with the culture from the right eye of Rabbit 4 developed patches of choroidoretinitis and were killed six weeks later. Rabbit 7 showed a purulent arthritis. Rabbit 8 was negative.

Three weeks after the original apical cultures had been made, organisms were removed with a sterile pipet, grown in broth for twenty-four hours, and injected into Rabbits 9, 11 and 12. Rabbit 9 developed a cloudy vitreous and died four days after inoculation. Necropsy revealed an arthritis. Rabbit 11 showed a pericorneal injection which gradually cleared up. Rabbit 12 had a

marked pericorneal injection three days after inoculation. The iritis gradually cleared. The vitreous of the right eye became increasingly hazy. The red reflex was lost entirely, and there was little pupillary light reflex (Fig. 2, *c* and Fig. 12). The animal died eight days after inoculation. Necropsy was negative except for the eye findings.

The patient's vision at the present time is 15/100.

CASE 2.—*Old iritis, myopia, detachment of retina.* D. S. D., a laborer, aged 35, had been losing vision in the left eye since 1902. Vision in the right eye was also markedly impaired. He was able to work but could not read small type. He had suffered from tooth abscesses as long as he could remember.

The left pupil was distorted from adhesions around the iris. There was a secondary cataract of the left eye. The right eye showed a large white area in the fundus with some detachment of the retina. Vision in the right was 12/200; on the left there was only light perception. The patient had a high grade myopia.

The general physical examination was negative. The urine showed no albumin, sugar or pus, and the Wassermann test was negative. Blood examination revealed: red cells, 4,160,000; hemoglobin, 80 per cent.; white cells, 6,800. The differential count revealed: polymorphonuclears, 64.5 per cent.;

Fig. 4.—Radiograph of tooth from which the culture in Figure 1 was made. The lesions shown in Figure 2 *b* and *c*, were produced by the intravenous injection of the streptococcus from this tooth.

polymorphonuclear eosinophils, 1 per cent.; polymorphonuclear basophils, 1 per cent.; small mononuclears, 23.5 per cent.; large mononuclears and transitionals, 10 per cent. A roentgenogram revealed ten pulpless teeth, only two of which showed alveolar abscesses. The upper left second molar was extracted on October 5. The patient did not return for the removal of the other pulpless teeth and has not been seen since. The cultures showed a profuse growth in pure culture of *Streptococcus fecalis*. Rabbits 67 and 68 were injected with the broth culture on October 6. No. 67 developed no eye lesions and showed only arthritis at necropsy. Rabbit 68 showed intense lacrymation and pericorneal injection twenty-four hours after inoculation. On October 31, the pericorneal injection was again present. The left eyeball protruded, the cornea was cloudy, and there was some loss of corneal epithelium (Fig. 8). The animal was killed. A purulent arthritis and vegetations on the endocardium were found.

CASE 3.—*Iridocyclitis.* H. F. N., a driver, aged 42, had suffered from attacks of rheumatism for years. Two years ago, his eyes had been red and painful for a few days. Four weeks ago, the right eye again became red and painful. Two days later the left eye was similarly affected. Just before the eye trouble began, a tooth had been extracted because it was abscessed.

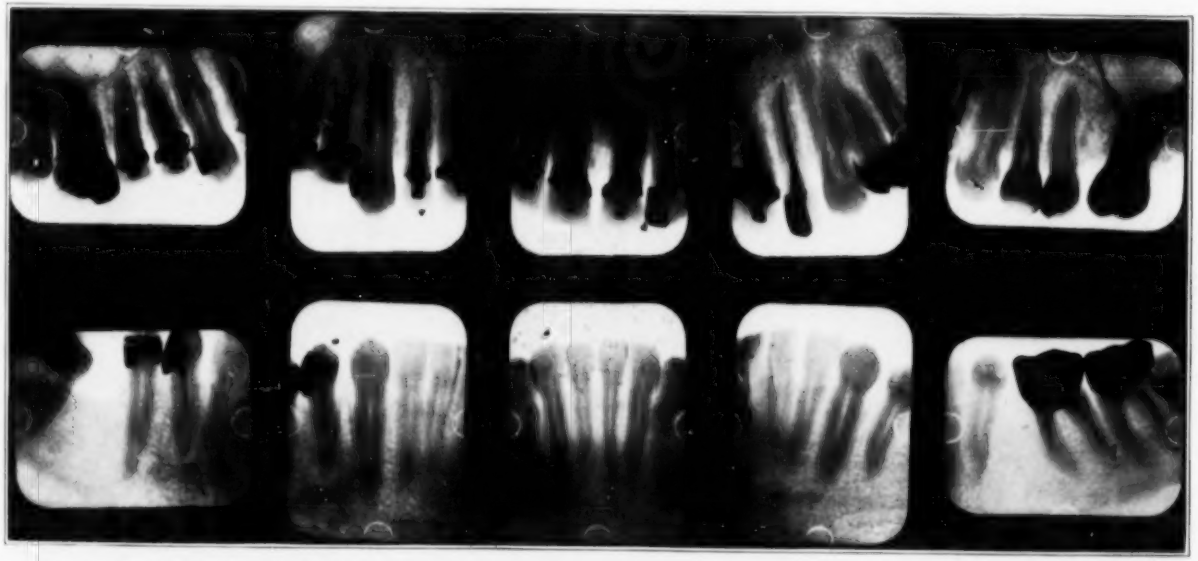

Fig. 5.—Teeth of patient E. O. M. (Case 8). The tooth showing the most marked roentgenographic evidence of infection is indicated by the arrow. This tooth showed a severe infection on culture, but the organisms recovered produced no eye lesions in rabbits. The lesion produced by the mixed cultures from the four upper incisors is shown in Figure *2 d*.

Examination of the right eye revealed iris pigment deposits on the anterior capsule of the crystalline lens and posterior synechiae. The iris was slightly muddy in appearance. The left eye was very much congested throughout the eyeball. The cornea was steamy, and there were clusters of keratitis punctata deposits on the back of the cornea. The vessels of the iris were large and could be well seen even through the murky medium of the anterior chamber. The vision in the right eye was 15/15; in the left eye, 15/100.

The general physical examination was negative. The tonsils were small. The blood count revealed: red cells, 4,312,000; white cells, 8,150; and the following differential count: polymorphonuclear neutrophils, 58.0 per cent.; polymorphonuclear eosinophils, 4.4 per cent.; polymorphonuclear basophils, 0.6 per cent.; small mononuclears, 25.2 per cent.; and large mononuclears and transitionals, 11.4 per cent. The urine showed a trace of albumin, a few pus cells and granular casts. The Wassermann test was negative. The roentgenogram revealed only one pulpless tooth, the upper right molar, the mesial root of which showed an alveolar abscess. A pure culture of *Str. salivarius* was obtained from the lingual root; the other roots were sterile.

On August 31, Rabbits 35 and 36 were inoculated intravenously with the broth culture. The following day No. 35 showed marked pericorneal injection and lacrymation. The next morning it was dead. No. 36 showed moderate pericorneal injection seven days after inoculation. On September 2, Rabbit 42 was inoculated with 5 c.c. of a broth subculture of the original culture. The

Fig. 6.—Tooth (indicated by arrow) from Case 12. The eye lesion shown in Figure 7 was produced by the intravenous injection of the streptococcus isolated from the pulp and root tip of the tooth. The first attack of iritis followed the placing of the large filling.

next morning the animal was dead. There was marked pericorneal injection of the right eye. Necropsy was otherwise negative.

Case 4.—*Uveitis following operation for secondary cataract.* M. V., a schoolgirl, aged 16, suffered from congenital cataracts which several years ago had been partly removed by needling, leaving a tough secondary membrane in each eye. One secondary cataract was removed with a good result. Six days after operation on the right eye in October, 1921, the patient had an attack of iridocyclitis; this developed into uveitis, which persisted until June, 1922. The infection became quiet, but the eye remained small and soft, in a condition of phthisis bulbi.

A roentgenogram, Sept. 1, 1922, showed alveolar abscesses around the roots of the upper and lower right first molars and the lower left first molars. Cultures of the upper right molars showed *Str. salivarius* and *Str. nonhemolyticus* I. The other two teeth showed a profuse growth of *Str. nonhemolyticus* I.

Rabbits 43 and 44 were inoculated, Sept. 2, 1922, with the mixed broth cultures. Rabbit 44 developed marked lacrimation and pericorneal injection, which gradually cleared up. Necropsy on September 9 showed a few abscesses in the kidneys and a purulent arthritis. Rabbit 43 showed similar changes in the eye and also some exudate in the anterior chamber. This rabbit has been

observed for the past nine months and has had numerous acute attacks of iritis at intervals of two to three weeks. The appearance of the eye in one of the less acute attacks is shown in Figure *2 f*.

Following the extraction of the teeth the infection of the right eye flared up.

Case 5.—*Iridocyclitis, uveitis, hyalitis.* G. R., an oil rig builder, aged 31, had had no serious illness except an attack of pneumonia in 1918. Recently he had nycturia. The right eye was struck by a nail in October, 1920. Six weeks later he noticed that he could not see well. In December, 1920, this eye became red and remained so for six weeks. He had had no vision in the right eye since that time. The left eye had also become red a few days before presenting himself.

An examination of the eye on May 22, 1922, showed on the right, evidence of trauma, uveitis and vitreous opacities. Vision was 15/20. The left eye showed a marked hyalitis.

The patient was in an excellent state of nutrition. The tonsils had been removed. The general physical examination was negative. A blood count revealed: red cells, 4,080,000; white cells, 12,950; and the following differential count: polymorphonuclear neutrophils, 68.0 per cent.; polymorphonuclear eosinophils, 2.04 per cent.; polymorphonuclear basophils, 0.4 per cent.; small mononuclears, 24.2 per cent.; large mononuclears and transitionals, 5.4 per cent. The urine showed albumin and numerous pus cells. The Wassermann test was positive. A dental radiograph showed an alveolar abscess around a root and one pulpless tooth. Cultures showed staphylococci and *Str. salivarius*. Four rabbits were injected with the broth cultures. None of the animals showed eye lesions.

Fig. 7.—The eye of Rabbit 152 following the intravenous injection of the streptococcus isolated from the pulp and root tip of tooth indicated by arrow in Figure 6.

Case 6.—*Acute glaucoma.* S. W., a housewife, aged 46, had been having some pain in the right eye for three years. In August, 1922, the pain became much more severe and the eye became red. The condition had been diagnosed and treated as iritis.

When seen on Sept. 12, 1922, the pupil of the right eye was dilated. There was a mild pericorneal injection. The intra-ocular pressure was 75 mm. (McLean tonometer). Vision was 15/200.

Since the intra-ocular pressure had ceased to respond to eserine, an iridotomy was performed on Jan. 17, 1923. When last seen, on March 22, 1923, the intra-ocular pressure was 39 mm. No local treatment had been given since Jan. 17, 1923.

The general physical examination on Sept. 22, 1923, was negative. The urine showed a few pus cells. The Wassermann test was negative. The blood count revealed: red cells, 4,150,000; white cells, 9,550; and the following differential count: polymorphonuclear neutrophils, 56 per cent.; polymorphonuclear eosinophils, 2.6 per cent.; polymorphonuclear basophils, 1.4 per cent.; small mononuclears, 35.2 per cent.; large mononuclears and transitionals, 4.8 per cent. A roentgenogram showed one alveolar abscess and two other pulpless teeth without apparent infection. Cultures of the extracted teeth showed *Staphylococcus aureus* and streptococci.

On September 14, Rabbits 57 and 58 were inoculated with the mixed cultures. On September 15, Rabbit 57 showed bilateral circumcorneal injection with exudate on the iris. The animal was killed. No other lesions were found. Rabbit 46 developed moderate pericorneal injection, which gradually disappeared. At necropsy, only a purulent arthritis was found.

Case 7.—*Glaucoma, recurrent iritis, high myopia.* E. B., a housewife, aged 46, had had several hemorrhages from the stomach in 1902. She complained of nycturia and frequent micturition during the day. She began to have pain in left eye four years before. An operation was performed on the left eye for glaucoma one year later. She gradually lost vision in the right eye. An operation for glaucoma was performed on the right eye, June, 1922. She had had an acute attack of iritis in the left eye for a week before presenting herself.

The right eye showed past iritis by the presence of an organized pupillary membrane which was not attached to the lens and which, when the pupil was contracted, would stretch out and impede the light. This was of long standing. Intra-ocular pressure was reduced to normal by iridotomy operation. In September, 1922, during the attack of iritis, there were some dots of keratitis punctata and pericorneal injection in the left eye.

The general physical examination was negative. Her tonsils were small, without apparent infection. Blood examination revealed: red cells, 4,020,000; white cells, 10,500; and a differential count; polymorphonuclear neutrophils, 73.4 per cent.; polymorphonuclear eosinophils, 2.6 per cent.; small mononuclears, 17.8 per cent.; large mononuclears, 6.2 per cent. Urine examination and the Wassermann test were negative. A roentgenogram showed nine pulpless teeth, two of which showed definite alveolar abscesses. The teeth were extracted in four groups.

One of two rabbits injected on Sept. 15, 1922, with the mixed cultures from the upper right and left central incisors developed iritis. No eye lesions were produced by the mixed cultures from the upper right second bicuspid and the first and second molars. Two rabbits (Nos. 69 and 70) developed iritis after the intravenous injection of the mixed cultures from the lower right second bicuspid and first molar. Rabbit 70 also developed meningitis. Cultures from the anterior chamber of the eye showed many colonies of streptococci and a few colonies of staphylococci. Rabbits 71 and 72 were injected with the cultures recovered from the eye of Rabbit 70. Both developed iritis and died the following day. Rabbits 74 and 75 injected with the cultures from the left lower first bicuspid and the second molar, also developed iritis. One died the following day; the other was kept for three weeks, when it showed marked bulging of both eyes with pericorneal injection. Rabbits 85 and 86 injected with a culture from the root tip of a tooth with a dying pulp developed acute iritis and meningitis.

Case 8.—*Recurrent iritis.* E. O. M., a clerk, aged 32, had had the first attack of iritis in 1905 and the second in 1909. Following this he had had frequent attacks at intervals of about one year. During the past two years he had suffered from iritis almost continuously in a subacute form. The patient said that the most severe attack he had ever had occurred while some dental work was being done. He had been confined to bed for four months in 1920 with rheumatism.

An examination of the right eye on May 20, 1922, during a period of active infection showed posterior synechiae, plastic exudates in anterior chamber and a small hemorrhage at the periphery of the iris. There was much pericorneal injection, deep and superficial. The intra-ocular pressure was normal. There was intense photophobia and lacrimation. The left eye showed no active infection, but posterior synechiae were present, indicating that there had been attacks of iritis in this eye also.

A physical examination, on Nov. 21, 1922, revealed a well compensated aortic insufficiency. The Wassermann test and urine examination were negative. A blood count revealed: red cells, 4,142,000; white cells, 8,350; and the following differential count: polymorphonuclear neutrophils, 68.2 per cent.; polymorphonuclear eosinophils, 7.2 per cent.; small mononuclears, 17.2 per cent.; large mononuclears, 7.4 per cent. A dental roentgenogram revealed nine pulpless teeth, only one of which showed a definite alveolar abscess (Fig. 5). The root tip of the lower left first bicuspid showed an infinity of colonies of a green-producing streptococcus in the brain agar cultures. The mixed broth cultures from this tooth and the upper left first bicuspid, however, produced no eye lesions in rabbits. The four upper incisors were removed at one operation. The upper right lateral was sterile even in broth, the left central and lateral showed *Str. salivarius*, and the central, *Str. fecalis*.

Two rabbits (Nos. 95 and 96) inoculated with the mixed cultures developed a marked iritis (Fig. 2 *d*). At necropsy one showed cloudy fluid in the joints

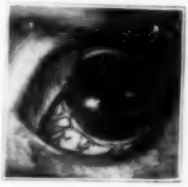

Fig. 8.—Retouched photograph of the eye of Rabbit 68, twenty-five days after the intravenous injection of organisms from infected teeth in a case of iritis (Case 2).

with an abscess of the kidney. The other had no lesion except that of the eyes. The upper and lower right second molars showed a profuse growth of staphylococci and streptococci. Two rabbits inoculated with the mixed cultures developed marked bilateral circumcorneal injection, with a purulent arthritis and abscesses in the kidney, voluntary muscle, and heart.

Case 9.—*Episcleritis.* J. W., a housewife, aged 31, had had "blood poisoning" in 1914 following childbirth. The appendix had been removed in 1908, and the tonsils in 1922. Her general health was good. She said that the eye trouble had begun three months previously, with itching of right eye lid and redness of the eye. The symptoms had disappeared under treatment, but had returned one week before. On examination the patient was found to be in an excellent state of nutrition. The heart, lungs and abdomen were negative. There were marked swelling and redness of the right lower lid, with circumcorneal injection and injection of the sclera of the right eye. Blood examination revealed: red cells, 4,000,000; white cells, 9,500; and the following differential count: polymorphonuclear neutrophils, 51.6 per cent.; polymorphonuclear eosinophils, 2.8 per cent.; small mononuclears, 42.8 per cent.; and large mononuclears, 2.8 per cent. The urine showed no albumin, sugar, pus or casts. The Wassermann test was not performed. The roentgenogram showed the upper right second bicuspid to be pulpless with no canal filling. The vitality of the adjacent molar

was questionable. These two teeth were extracted. The bicuspid showed a profuse growth of staphylococci and *Str. fecalis.* The molar also showed streptococci and staphylococci.

Rabbits 87 and 88 inoculated with the mixed cultures died forty-eight hours later. Rabbit 87 showed a marked hemorrhagic iritis with fluid in the anterior chamber (Fig. 2 *c*) and multiple small abscesses in the kidneys. Rabbit 88 showed a few hemorrhages in the iris and sclera and kidney abscesses.

CASE 10.—*Monocular acute conjunctivitis with corneal abscesses, iritis.* J. P., a clerk, aged 60, had been blind for three years. There had been no pain or inflammation, but vision had been very dim and gradually became worse eight years previous to this time.

Examination on Nov. 10, 1921, showed a fully developed cataract in the right eye, with good light projection. There was a partly absorbed cataract, with calcification in the left eye. This was removed, and the eye went on to perfect healing with a vision of 15/30. The right eye was operated on without complication except that it remained red longer than the usual time. In six weeks it had become quiet. Vision after injection was 10/30. On Nov. 22, 1923, the right eye was very painful and red, with much pus in the conjunctival sac. There were numerous small grayish ulcers in the cornea, superficial and gray striations in the posterior layers, with a slightly congested iris. There were also small grayish abscesses in the corneal tissue. For days later there was exudate in the anterior chamber. The conjunctivitis probably followed the breaking of a small corneal abscess and might have come from within.

The general examination, on Nov. 25, 1922, was negative. The blood count revealed: red cells, 4,140,000; white cells, 10,200; and the following differential count: polymorphonuclear neutrophils, 65.0 per cent.; polymorphonuclear eosinophils, 2.4 per cent.; polymorphonuclear basophils, 0.8 per cent.; small mononuclears, 23.4 per cent.; large mononuclears, 8.4 per cent. The urine showed a trace of albumin and sugar. The Wassermann test was negative. The dental roentgenogram showed one broken tooth with bone destruction around the root end. Seven other teeth showed extensive pyorrhea.

Two rabbits were inoculated on Nov. 26, 1922, with the mixed culture from four of the extracted teeth. On November 27, Rabbit 104 had developed a marked pericorneal injection of the right eye, which persisted until the animal was killed four days later. Necropsy revealed endocardial vegetations, kidney abscesses and purulent arthritis. Rabbit 105 developed a slight injection of the right eye, with similar necropsy findings. Rabbits 101 and 102 were inoculated with the mixed cultures from the remaining extracted teeth. Rabbit 101 developed a hemorrhagic iritis, and the other a marked circumcorneal injection of one eye. Both animals showed abscesses of the kidneys and a purulent arthritis at necropsy.

CASE 11.—*Ulceration of cornea.* S. K., a farmer, aged 62, had suffered from rheumatism at intervals for thirty years. He had also had "lumbago" at times. His present trouble began on Aug. 1, 1922, with pain and redness of the right eye, which his physician thought was due to an iritis. At the same time he had an eruption on the right side of the face and body. The eye improved under treatment, but the symptoms returned later and have persisted. Examination of the right eye showed an ulcer in the superficial layers of the cornea in the center of the pupil. There is no sign of iritis at present. There was much pus in the meibomian glands and thickening of the lids. Vision was 15/200. The tonsils were small. The general physical examination was negative. Blood count revealed: red cells, 4,144,000; white cells, 9,550; and the following differential count: polymorphonuclear neutrophils, 72.2 per cent.; polymorphonuclear eosinophils, 3.8 per cent.; polymorphonuclear basophils, 1.2 per cent.; small mononuclears, 19.2 per cent.; and large mononuclears, 3.6 per cent. The urine contained no albumin or sugar. The Wassermann test was anticomplementary. The dental roentgenogram showed multiple pulpless and infected teeth.

Two rabbits injected from three of the extracted teeth developed no eye lesions. The lower left central and lateral incisors showed *Str. fecalis* in pure culture. Rabbits 134 and 139 were inoculated with these mixed cultures. Rabbit 134 developed an iritis of one eye which gradually cleared up. Necropsy revealed only a purulent arthritis. Rabbit 139 developed a marked bilateral pericorneal injection, which continued until the animal was killed ten days later. The only necropsy finding was cloudy fluid in the joints.

The patient had a complete recovery with vision 13/15. He was given subcutaneous injections of milk also, so it is difficult to determine just what effect the extraction of the teeth had.

CASE 12.—*Uveitis.* Mrs. F. T., a housewife, aged 43, had had typhoid fever in 1914 and rheumatism during the past year. Her eye trouble began in 1912, with a severe attack of iritis with almost complete loss of vision in the left eye.

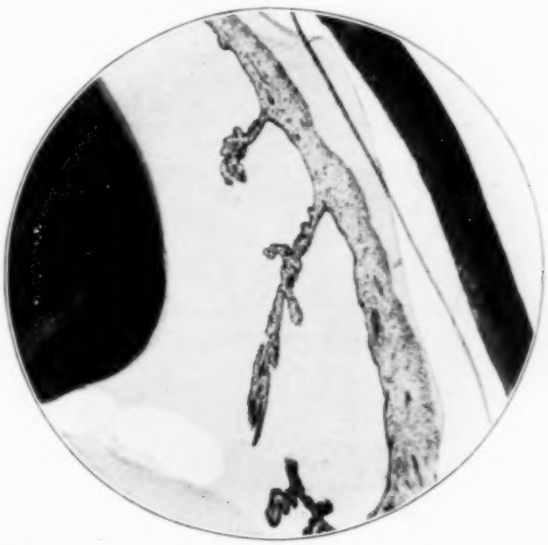

Fig. 9.—Portion of iris and ciliary body of eye of Rabbit 95 (Fig. 2 *d*).

A second attack occurred in 1916. She had no further trouble until December, 1922, when iritis again occurred in the left eye, followed by another attack in January, 1923. When first seen on March 1, 1923, there was no light perception, and the eye showed that the whole uveal tract had been involved. The patient said that a large filling had been placed in the right lower first molar in 1912. The tooth became very painful. The filling was removed to "let the gas out" and replaced. The first attack of iritis developed soon after the tooth trouble. An examination of the right eye showed no light perception, posterior synechiae, without active infection. The vision in the left eye was 20/20. There were posterior synechiae, but no inflammation.

The patient was undernourished. The tonsils were small. The general physical examination was otherwise negative. Blood count revealed: red cells, 4,300,000; white cells, 8,700, and the following differential count: polymorphonuclear neutrophils, 66.4 per cent.; polymorphonuclear eosinophils, 2.6 per cent.; polymorphonuclear basophils, 0.8 per cent.; small monoru-

clears, 28.2 per cent., and large mononuclears, 2.0 per cent. All the upper teeth had been extracted. A roentgenogram showed no apparent bone infection in the upper jaw. There were no pulpless teeth in the lower jaw. The right lower first molar had a large silver filling, was tipped forward, and had a pocket around it (Fig. 6). The tooth responded, however, to tests for vitality. This tooth was extracted. On opening the pulp chamber under sterile precautions, it was found that the pulp chamber had been encroached on by secondary dentine formation. The nerve was injected and edematous and showed a pure culture of *Str. mitis*. The same organism was obtained in the culture of the root tips. Rabbits 152 and 153 were inoculated with the mixed cultures from the pulp and root tip on Feb. 2, 1923. Rabbit 152 developed an extreme pericorneal injection which was less marked the following day. On February 7, the circumcorneal injection had returned in the right eye. There

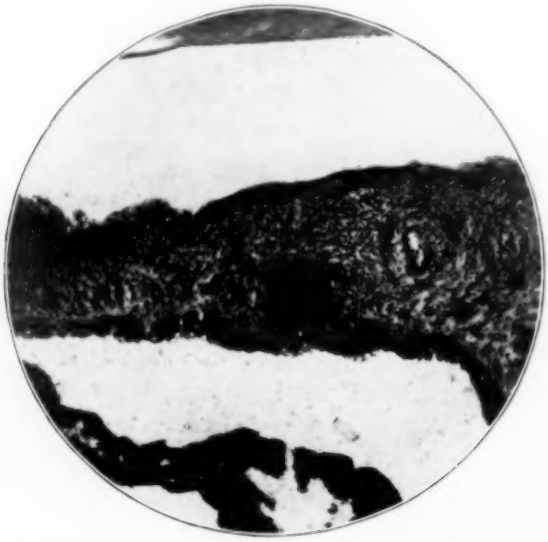

Fig. 10. —Iris showing area of small round cell infiltration.

were multiple hemorrhages in the iris and cloudy fluid in the anterior chamber (Fig. 7). Necropsy revealed also abscesses of the kidneys, white streaks in the muscles and a purulent arthritis. Rabbit 153 showed only cloudy fluid in the joints.

Case 13.—*Iridocyclitis, uveitis, hyalitis.* J. R., a salesman, aged 22, had a "nervous breakdown" in October, 1922. He had never been ill before. In December, 1922, he noticed that the vision in the right eye was blurred. The condition improved, but the dimness of vision recurred and had grown steadily worse. The patient could recognize hand movements at 0.5 meter. The eye was a little softer than usual. The back of the cornea was almost covered with small round dots of exudate (keratitis punctata). The eyeball was moderately red and the pupil round, but there were some posterior synechiae. The vitreous was one mass of floating opacities. The patient was well nourished. The tonsils were large, but no free pus could be expressed. The general physical examination was otherwise negative. The blood count showed

5,824,000 red cells, 7,900 white cells, hemoglobin 116 per cent., and the following differential count: polymorphonuclear neutrophils, 63.2 per cent.; polymorphonuclear eosinophils, 2 per cent.; polymorphonuclear basophils, 0.2 per cent.; small mononuclears, 31.0 per cent., and large mononuclears, 5.6 per cent. The roentgenogram showed only one pulpless tooth which had a large cavity and an alveolar abscess. A culture of the root tip showed a staphylococcus and *Str. salivarius*. The organisms grew only near the bottom of the culture tube.

Rabbits 176 and 177 were inoculated with the cultures of root tips and curettings on March 3, 1923. Rabbit 176 showed pericorneal injection, which gradually increased in intensity. At necropsy on April 10, only a purulent arthritis was found. Rabbit 177 developed no eye lesions and showed only a healing arthritis at necropsy. Rabbits 178 and 179 were injected on March 3, with the cultures from the curettings of the tooth socket only. Three hours after

Fig. 11.—Eye showing marked infiltration of choroid.

inoculation both animals showed an extreme pericorneal injection. Rabbit 178 continued to have a moderate pericorneal injection, and as late as May 3 had an acute attack of iritis. Rabbit 179 was killed twenty-five days after inoculation and showed only a healing arthritis.

Case 14.—*Acute iritis with arthritis.* E. E., a housewife, aged 38, said that her present trouble had begun two weeks previously with pain in most of the large joints. There was no swelling or redness. One week before she noticed an eruption on the forearms and back of the neck, beginning as red macules which gradually spread as they cleared in the center. For several days her eyes had been red. The patient was much undernourished. The skin eruption appeared to be an erythema multiforme. Her tonsils were small. The submental glands were large and painful on pressure. There was some excess fluid in the right knee. The larger joints were painful on motion. The left eye presented the picture of a mild iritis. The blood count showed: red cells, 3,056,000; white cells, 10,750, and the following differential count: polymorpho-

nuclear neutrophils, 70.4 per cent.; polymorphonuclear eosinophils, 1.4 per cent.; polymorphonuclear basophils, 0.8 per cent.; small mononuclears, 19.4 per cent., and large mononuclears, 8.0 per cent. The urine contained a trace of albumin but no sugar, pus or casts. The Wassermann test was negative. A roentgenogram revealed fifteen pulpless teeth, several of which showed alveolar abscesses. Rabbits 190 and 193 were inoculated on March 28, 1923, with the mixed cultures from six extracted teeth. Both developed extreme pericorneal injection within a few hours. Rabbit 190 was killed on April 4, and showed purulent fluid in the joints, endocardial vegetation and a few kidney abscesses. The pericorneal injection in Rabbit 193 had disappeared the day following the

Fig. 12.—Vitreous of eye shown in Figure 2 *c*. Note the infiltration of cells in the vitreous humor.

inoculation. It was again present on March 3, when the animal was killed. A pure culture of a green-producing streptococcus was recovered from the iris. A meningitis and purulent arthritis were also present. Four other animals were inoculated with cultures from other teeth. Two developed iritis, and all showed a purulent arthritis at necropsy.

Following the extraction of the first teeth the patient had an exacerbation of the arthritis. The iritis and skin eruptions disappeared within a few days. The arthritis had cleared entirely within four weeks.

Case 15.—*Recurrent iritis with arthritis.* L. S. L., a housewife, aged 47, had always enjoyed excellent health until recently. During the past year she had

suffered from stiffness in the right knee and frequent attacks of redness of the right eye, lasting from one to three days. The patient was in an excellent state of nutrition. There was moderate pericorneal redness of the right eye. The tonsils were small. The blood count showed 7,700 white corpuscles, and the following differential count: polymorphonuclear neutrophils, 73.0 per cent.; polymorphonuclear eosinophils, 1.0 per cent.; polymorphonuclear basophils, 0.4 per cent.; small mononuclears, 20.6 per cent.; large mononuclears, 5.0 per cent. There was a trace of albumin and numerous pus cells in the urine. The Wassermann test was negative. A roentgenogram showed marked pyorrhea around the lower first molar with interradial bone absorption. The tooth contained a large filling. *Str. mitis* was recovered from the root tips and a green-producing streptococcus from the pulp in pure culture. Rabbits 164 and 173 were inoculated with the streptococcus recovered from the pulp. Both animals developed a pericorneal injection and at necropsy showed many white streaks in the muscles and a purulent arthritis. The two animals inoculated with the cultures from the root tip developed no eye lesions. Many abscesses in muscles and kidneys were found at necropsy.

The patient's joint and eye symptoms disappeared quickly after the extraction and have not recurred.

RENAL INJURY PRODUCED IN RABBITS BY DIETS CONTAINING MEAT*

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In a recent communication [1] we described the atherosclerosis which is produced in rabbits that are fed diets rich in meat proteins. The kidneys of the same rabbits presented abnormalities which form the subject of this paper.

The composition of the diets and the selection and care of the animals was described in the previous paper in the following words:

> The animals were fed diets containing two different concentrations of protein. Lean beef muscle mechanically freed of fat and then dried and powdered [2] was the chief source of protein. Ordinary white bread flour mixed in equal parts with bran, supplied carbohydrate and roughage. The first diet was made by stirring together 1,000 gm. of the powdered beef; 2,000 gm. of the flour, bran mixtures; 20 gm. sodium chlorid; 50 gm. baking powder and enough water to produce a stiff dough. The latter was then spread thickly in oiled pans and baked in an oven at about 180 C. until a dark brown crust had formed.
>
> The second diet contained 500 grams of powdered beef, 2,000 gm. of the flour-bran mixture, 20 gm. of sodium chlorid and 50 grams of baking power. It was prepared for feeding in the same way as the first diet.
>
> An analysis for nitrogen, by the Kjeldahl method, of the powdered beef and of the two diets, gave the following values:
>
> | | |
> |---|---|
> | 100 gm. dried powdered beef..... | = 13.0 gm. N. |
> | 100 gm. first diet..... | = 5.8 gm. N. |
> | 100 gm. second diet..... | = 4.3 gm. N. |
>
> Multiplying these nitrogen figures by 6.25 gives the following protein content:
>
> | | |
> |---|---|
> | Dried powdered beef..... | = 81.2% Protein |
> | First diet..... | = 36.2% Protein |
> | Second diet..... | = 26.8% Protein |
>
> In addition to this food, the rabbits were each allowed about 100 gm. of greens once a week.
>
> The animals were obtained from fanciers who had taken special pains to raise them in clean, light, well ventilated pens. During the feeding experiments they lived in pens which had previously been made scrupulously clean and which were kept clean thereafter. Some of the rabbits were housed together in small groups. Many others lived throughout the experiment in

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1. Newburgh and Clarkson: The Production of Atherosclerosis in Rabbits by Feeding Diets Rich in Meat, Arch. Int. Med. **31**:653 (May) 1923.

2. This material was obtained from the Digestive Ferments Co., Detroit.

individual cages. These cages were located in an unheated shed which protected the animals from wind and rain but which afforded them ample sunshine and ventilation. The date of birth of many of the rabbits was known and we were thus able to determine whether age played a part in the causation of the lesions.

The first group, consisting of eight animals to which the diet containing meat was fed, were brought to the laboratory when half grown. For the next two months they were fed the stock laboratory diets. At the end of this period they appeared to be in excellent condition and in no case did the urine contain albumin. They then began to eat the experimental diet containing one part of the dried beef to two parts of the flour. On June 4, 1919, one week after the beginning of the experiment, the urines of five of the rabbits were examined. Three were alkaline, two neutral, and all gave definite reactions for albumin. The sediments contained no abnormalities. On June 17, a few hyaline and granular casts were found in some of the specimens examined. By July 9, six weeks after the beginning of the experiment, both albumin and casts were found in the urine of every rabbit in the group.

Evidence was thus obtained which indicated that the ingestion of a meat containing diet by rabbits will result, within a few weeks, in an abnormal state of the kidneys.

One of the eight rabbits lived five months, and two of them lived seven months on the diet.

The first of these rabbits was found on Oct. 15, 1919, lying on its side and was unable to maintain the standing position. No twitching was observed, and the breathing was normal. It weighed 2,090 gm. It was killed by a blow on the head, and necropsy immediately performed. The bladder urine was slightly acid to litmus, had a specific gravity of 1,020, contained 0.7 per cent. albumin (Esbach), and the sediment showed many granular and hyaline casts but no leukocytes or red blood corpuscles. The kidneys weighed 25.5 gm.;[3] the surface was smooth and dark red. The cut surface was dark, congested and "glassy," with a few white streaks in the cortex. The aorta showed extensive atherosclerosis. The liver was firmer than normal and on section gave the appearance of cirrhosis. The remainder of the organs were grossly normal. Nothing suggesting infection as a cause of death was seen.

The second of these three rabbits developed an increasing indifference to his surroundings during the few days preceding his death, accompanied by a gradual loss of appetite. On Jan. 6, 1920, he refused food entirely. He weighed 2,310 gm. He was killed by bleeding. The bladder urine showed a well marked albuminuria and numerous granular and hyaline casts but no leukocytes or red blood

3. The kidneys of normal adult rabbits weigh from 5 to 6 gm. per kilogram.

cells. The kidneys weighed 22 gm., but presented no definite abnormalities to the unaided eye. The aorta showed extensive atherosclerosis. The remainder of the organs appeared to be normal, and no evidence of infection was seen.

The third rabbit, on Dec. 24, 1919, was limp, trembling, dyspneic and unable to maintain the erect position. He weighed 2,380 gm. He was killed by a blow on the head. The bladder urine was dark, contained a large amount of albumin, many hyaline, granular and cellular casts, but no leukocytes or red blood cells. The kidneys weighed 32.5 gm., and were dark brownish red. The capsule stripped

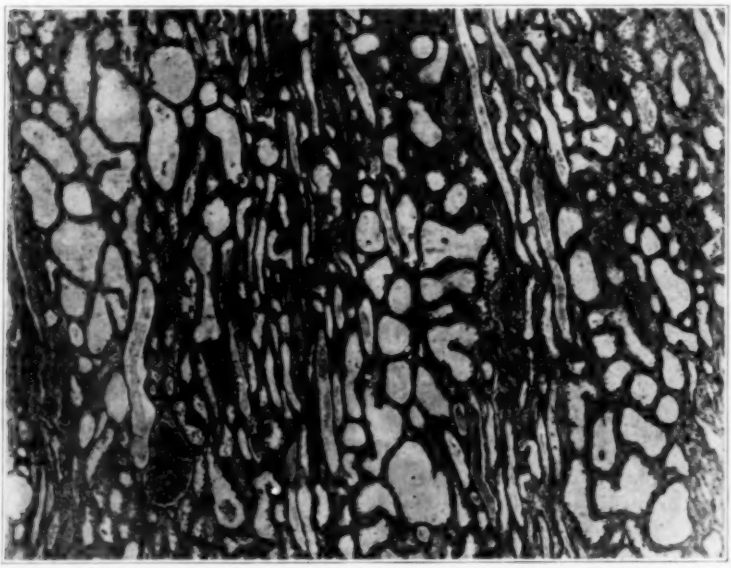

Fig. 1.—Midcortical portion of the kidney of a rabbit that had eaten a diet containing 36 per cent. of protein for seven months. The tubules are greatly dilated and their lining epithelium is much flattened. The glomerulus is apparently normal. No fibrosis is to be seen. Casts are numerous.

easily, leaving a smooth surface. On section, the organ dripped blood. The cortex protruded above the general surface, was "glassy" and presented many minute hemorrhagic points and streaks. The aorta showed extensive atherosclerosis. The liver was firmer than normal and on section presented the markings suggestive of cirrhosis. The other organs were normal, and no evidence of infection was noted. These gross evidences of disease of the kidneys were confirmed by microscopic examination. Figure 1 is a photomicrograph of a section from the kidney of the third rabbit.

This feeding experiment, performed in 1919 with a diet containing 36 per cent. of protein, was repeated in 1922. The results obtained in the earlier series were confirmed by the data from the later group of rabbits. Figures 2, 3, and 4 are photomicrographs of the kidney of one of these rabbits (No. 140) of the 1922 group that lived on the diet for twenty-seven weeks.

NEPHROPATHY OF RABBITS WHOSE DIET CONTAINED 27 PER CENT. OF PROTEIN

The nephropathy described above occurred in rabbits that had been eating a diet with a protein content of about 36 per cent. It was

Fig. 2.—Subcapsular portion of cortex of a rabbit that had eaten a diet containing 36 per cent. of protein for about six months. Dilatation of tubules and flattening of their lining membrane is well marked but not so extreme as that shown in Figure 1. The glomeruli are normal and fibrosis is absent. Casts are numerous.

accordingly of interest to study the kidneys of rabbits whose food contained less protein. A large number of animals whose diet contained 27 per cent. of protein were available for this purpose. These animals may be divided into two lots—Group A containing the rabbits that lived on the diet less than twenty-four weeks and whose kidneys in no case showed chronic lesions attributable to the diet; and Group B, consisting of animals that took the diet from twenty-four

to fifty-nine weeks, in 75 per cent. of which chronic renal lesions were seen.

Group A.—There were thirty-three animals in this group. Nine of them died of pneumonia early in the experiment. In the remainder the only gross abnormality regularly revealed by necropsy was the presence of kidneys which were considerably larger than normal. In every instance in which bladder urine was obtained at necropsy there existed a marked albuminuria, and many casts were found in the

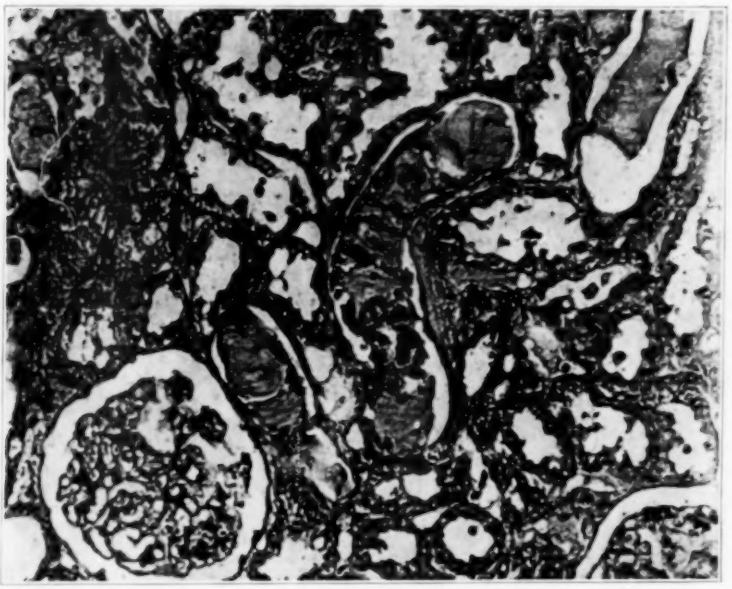

Fig. 3.—Higher magnification of a portion of the field seen in Figure 2 to show in particular the character of the casts.

sediment. The microscopic examination of the kidneys of the animals in which no pneumonia was found regularly disclosed varying degrees of acute parenchymatous injury. The cells of the convoluted tubules appeared to have suffered most. In some cases the lumina of the tubules were closed by the swelling of the cells. Extensive desquamation, vacuolization and granular degeneration were seen in the convoluted tubules of most of the kidneys. Casts were always a prominent feature, and sometimes they were numerous. Minor changes in the glomeruli were sometimes noted, but no true acute glomerulitis was seen.

Group B.—This group contained twelve animals. The kidneys of nine of them showed extensive chronic lesions, most marked in the cortical portion of the tubules. The microscopic picture presented by these kidneys closely resembled that already described (Figs. 1, 2, 3 and 4) for the animals that had lived from five to seven months on a diet containing 36 per cent. of protein.

In both groups the nephropathy was notable for its diffuse character. The dilatation and atrophy of the tubules frequently extended with varying degrees of intensity across the whole section; or, in a

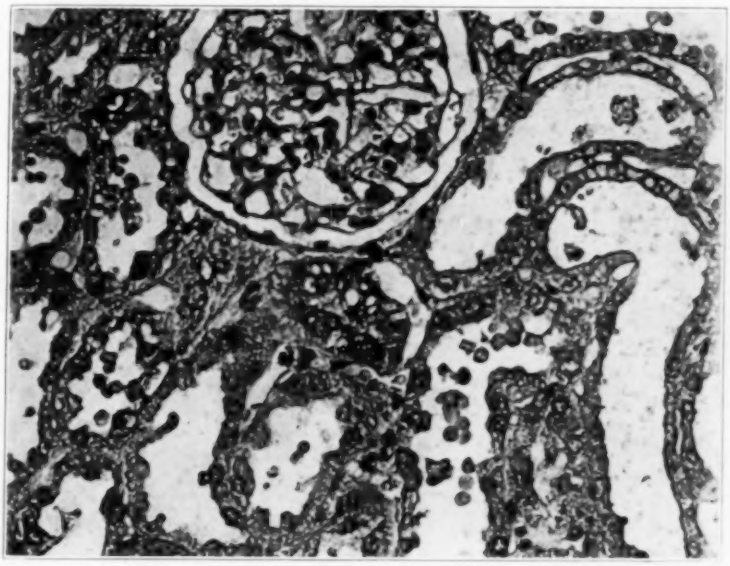

Fig. 4.—Still higher magnification of a portion of the field seen in Figure 2, showing the presence of red blood corpuscles in the lumina of the tubules, and the flattening, granulation, vacuolization and desquamation of the tubular epithelium.

few instances, was broken up into broad irregular patches separated by a few tubules whose cells were only slightly or not at all atrophied. Nowhere were the cells of the tubules normal. The glomeruli showed no injury or minor degrees of injury and were not scarred. The dilated tubules were not embedded in fibrous tissue, nor was there any general increase in fibrous tissue. The disease, from the histologic point of view, appeared to be restricted to the lining cells of the tubules. In rabbits that had eaten the diet only a few weeks, these cells showed the well-known picture of acute and subacute degeneration. The renal

tubules of rabbits that had lived on the diet for months showed much desquamation and a lining membrane whose cells had undergone varying degrees of flattening, finally being changed into pavement epithelium. In some tubules the lining membrane had entirely disappeared.

This progressive atrophy of the renal tubules was unattended by any significant changes in the glomeruli or blood vessels or interstital tissue that could be recognized by means of the microscope.

Figures 5 and 6 are photomicrographs of the kidneys of two of these rabbits (Nos. 67 and 118) that had been on the diet six and one half and eight months, respectively.

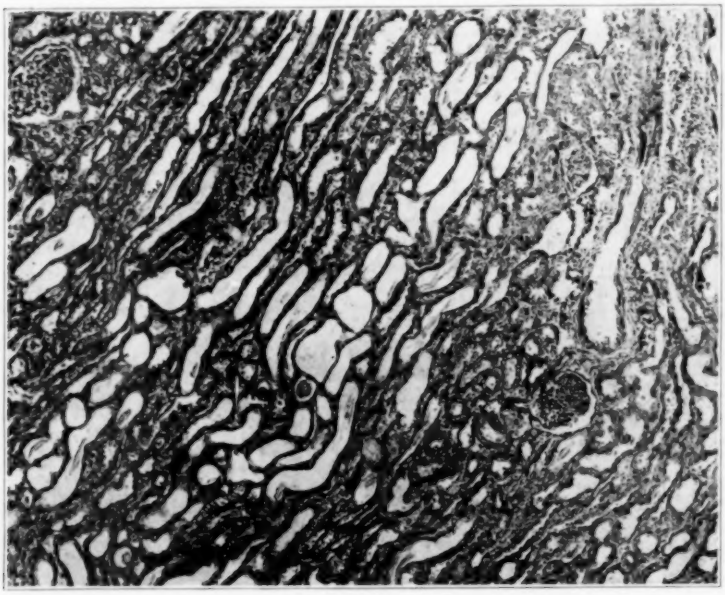

Fig. 5.—Cortical portion of the kidney of a rabbit that had eaten a diet containing 27 per cent. of protein for six and one half months. In general, the changes closely resemble those seen in Figure 1. There is the same widespread dilatation of tubules without fibrosis or scarring of glomeruli.

The kidneys of three of the rabbits in Group B that had been on the diet as long as any of the group did not show these chronic tubular changes. This brings up the question whether the tubular dilatation and atrophy found in 75 per cent. of the kidneys was caused by the diet. It is well known to laboratory workers that the kidneys of untreated rabbits are frequently abnormal. If one inspects carefully the kidneys of laboratory rabbits, one will find many whose surface

is indented by bluish stellate scars and deep pits or grooves. The number of these depressions is highly variable. Under the microscope these pits are seen to be the outer surface of a band of contraction, consisting of a strip of fibrous tissue in which are found one or several more or less completely scarred glomeruli and several atrophied tubules. These lesions are always definitely focal in character, occurring as sharply circumscribed bands extending from the capsule, through the cortex deep into the medulla. The glomeruli and tubules beyond the band are usually normal, and both atrophy and scarring are restricted to the band.

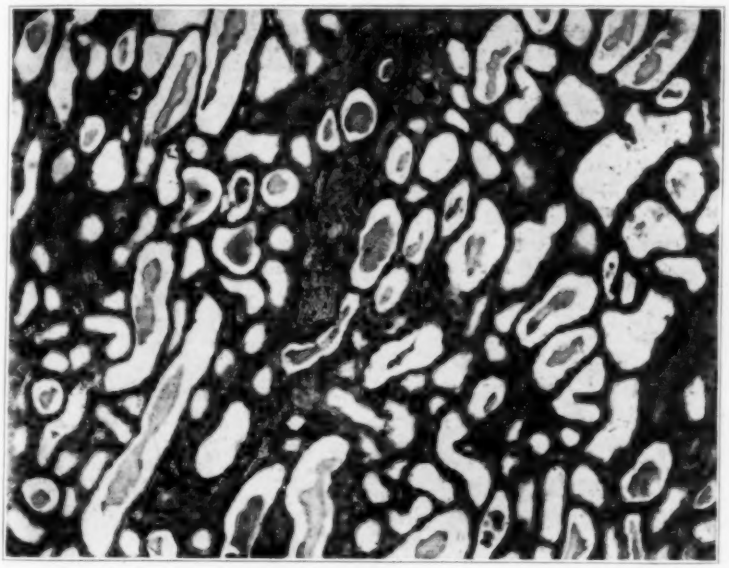

Fig. 6.—Lower cortical portion of the kidney of a rabbit that had eaten a diet containing 27 per cent. of protein for eight months. Here again the widespread dilatation of tubules is the characteristic abnormality.

KIDNEY LESIONS IN RABBITS LIVING ON A STOCK DIET

In order to control our work properly, it was necessary to determine how often such lesions were found in rabbits that lived in the laboratory for many months on a stock diet, and whether such lesions in control rabbits ever were widespread and diffuse; that is, whether the diffuse tubular disease seen in the kidneys of the Group B rabbits could have been caused by conditions resulting from prolonged residence in the laboratory in the absence of the meat diets.

For this purpose nineteen rabbits were set aside in a stock cage and given the ordinary laboratory care and food. No attempt was made to protect these animals from infection; on the contrary, we tried to emphasize the effect of the usual laboratory infections on the kidneys by leaving infected rabbits in the pen instead of removing them and isolating them according to our usual procedure. Several of the animals died of pneumonia within the first few weeks. Many of the others acquired "snuffles" early in the experiment. Three of the animals had received intravenous injections of bacteria for the purpose

TABLE 1.—*Data From Thirteen Control Rabbits that Lived Six Months or More*

No.	Duration, Weeks	Weight at Necropsy, Gm.	Kidney			Notes
			Weight, Gm.	Gross Appearance	Microscopic Examination	
1	25	1,670	8	.....	.....	
5	26	1,200	11	No scars	No abnormalities	Severe diarrhea
12	45	1,010	13	Very few small scars	No abnormalities	Purulent bronchopneumonia; empyema
37	50	1,450	13	Many scars	Scattered small areas of round cell infiltration	
52	57	2,650	13	No scars	No abnormalities	Bronchopneumonia; petechial hemorrhages of liver; mange
68-X	40	870	10	No scars	No abnormalities	Prolonged snuffles; great emaciation
71	64	3,000	13	Many deep scars	One band of atrophy and fibrosis; casts in this band; otherwise no abnormalities	Severe mange
74	26	940	9	Very few scars	No abnormalities	Emaciation
81	30	1,630	15	No scars	No abnormalities	
83	51	1,380	13	Many scars	Few casts; otherwise normal	Six intravenous injections of Streptococcus hemolyticus; mange; emaciation
84	40	1,110	11	No scars	No abnormalities	Six intravenous injestions of diphtheria bacilli; mange; emaciation
86	22	1,370	13	No scars	Few small areas of moderate dilatation of tubules	Six intravenous injections of killed typhoid bacilli; six intravenous injections Streptococcus hemolyticus; caseous pneumonia; synechia cordis
A-X	58	1,727	10			

of producing immune serums several months before they were set aside as controls. The group as a whole was undernourished and listless. Skin diseases became prevalent, and in some cases resulted in suppuration. All but one of the animals eventually died of infection. Thirteen of the rabbits lived six months or longer, but unfortunately the kidneys of two of them were lost through a technical error.

Table 1 presents the significant data in regard to these thirteen animals. It will be seen that scarring of the surface of the kidney was fairly common, but the microscope showed dilatation of tubules in only one case. The photomicrograph of this kidney (Fig. 8) demonstrates the sharply focal character of this lesion and the entire

absence of such lesions in other parts of the field. There is a striking difference between the pathologic process in this kidney and that found in the meat eating rabbits (Figs. 1 to 7).

The contrast between the diffuse character of the tubular dilatation, the absence of glomerulitis and the absence of scar tissue in the kidneys of the meat fed animals, when compared with the focal tubular dilatation, the presence of scarred glomeruli and of bands of fibrous tissue seen in the controls, is so great as to make it certain that the

Fig. 7.—Higher magnification of a portion of the field seen in Figure 5 to show the changes in the lining membrane of the tubules. Some of the tubules which show the greatest dilatation appear to have lost their parenchymatous cells.

nephropathy found in the kidneys of at least the majority of the meat eating rabbits was a product of the diet.

Table 2 contains brief notes about all the rabbits that lived on the meat containing diets for twenty-four or more weeks—sixteen rabbits in all. The renal tubules of twelve of them showed atrophy. In nine (B3, A4, 140, 61, 67, 88, 77, 78 and 118) of these twelve rabbits, the histologic picture presented by the kidney was such that it could not easily be confused with the scarring and atrophy occasionally

found in untreated animals. In the remaining three of these twelve rabbits, the nephropathy appeared to be at least in part attributable to conditions unrelated to the diet; and it was impossible to determine how much was caused by the diet and how much was "spontaneous."

The profound effect of the diet on the state of the tubular epithelium is also determined by contrasting the number of cases of dilatation and atrophy of tubules occurring in the control rabbits with the number of cases of such atrophy found among the animals that had eaten the meat-containing diets for twenty-four weeks or

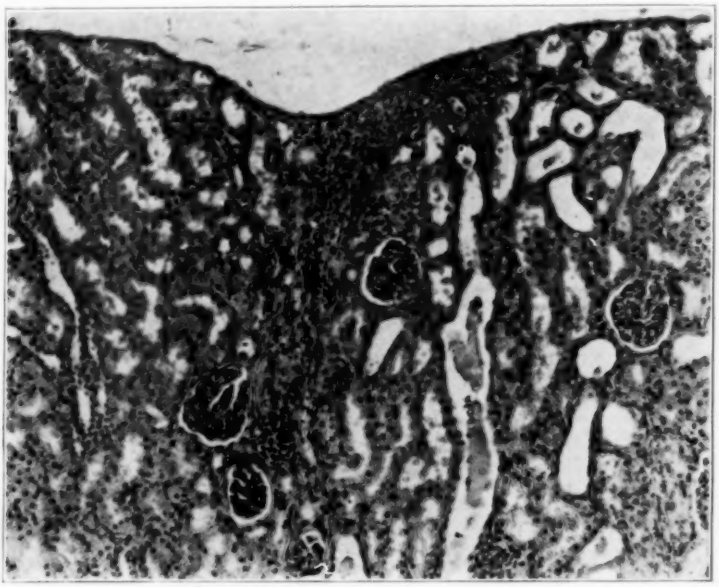

Fig. 8.—Character of the lesions which are found in some control rabbits. A band of fibrous tissue has caused retraction of the outer surface of the kidney, with scarring of the glomeruli in its path. The sharp separation of the normal tissue in the left half of the field from the portion containing the dilated tubules is clearly seen. The focal character of the tubular dilatation seen in this kidney contrasts strikingly with the diffuse and widespread dilatation of tubules presented in Figures 1, 2, 5 and 6.

more. In making this comparison, no account is taken of the distribution of the tubular dilatation—whether sharply restricted, patchy or diffuse—nor of the presence or absence of other lesions. It is a simple comparison between the percentage of "treated" animals whose kidneys showed tubular atrophy with the percentage of control animals whose kidneys showed tubular atrophy. When this is done it is found that

TABLE 2.—*Data From Sixteen Rabbits Fed a Meat-Containing Diet for More Than Six Months*

No.	Duration, Weeks	Weight at Necropsy Gm	Kidney Weight, Gm.	Kidney Gross Appearance	Microscopic Examination
Four Rabbits Whose Diet Contained 36 per Cent. Protein					
B 3	30	2,870	22	Coarsely granular surface; no deep pits	Great atrophy and dilatation of tubules, widespread and not related to the small patches of fibrosis; many casts
A 4	30	2,380	32	Surface smooth; no scars	Great atrophy and dilatation of tubules uniformly distributed; few small areas of fibrosis; many casts
138*	24	3,320	20	Few old scars	Many areas of round cell infiltration; no chronic changes
140	27	2,550	28	Occasional small scars	Diffuse tubular atrophy throughout cortex; intense parenchymatous injury; many casts
Twelve Rabbits Whose Diet Contained 27 per Cent. Protein					
26	44	2,170	22	Some stellate scars	Irregular areas of round cell infiltration; bands and patches of contraction and atrophy; no broad areas of tubular atrophy
27	41	1,920	23	Many irregular depressed scars; a number of narrow yellow streaks extend from capsule to medulla	Several bands, each consisting of scarred glomeruli and dilated tubules embedded in fibrous tissue; in lower cortex most of the tubules show extreme atrophy; the lumina of the remaining tubules are closed by greatly swollen vacuolated cells whose protoplasm is granular and whose nuclei are pienotic; many casts
60	50	2,600	15	A number of irregular purple scars	No chronic changes; scattered casts
61	32	2,000	30	A few small scars	No bands of scarring; no scarred glomeruli; uniform high grade dilatation and atrophy of tubules, except in outermost portion of cortex where the cells are swollen and granular; many are vacuolated; many casts
67	28	1,750	29	A few scars	No bands of contraction; uniform marked dilatation and atrophy of tubules; glomeruli show no changes; much swelling and desquamation of tubular epithelium; many casts
88	29	1,680	16	Many pitted scars on section; many pale yellow bands seen in medulla	Two small cortical bands of contraction; most of the tubules in the lower cortex show moderate atrophy and dilatation; signs of acute parenchymatous injury not marked
77	26	1,477	22	Few deep scars	No bands of contraction; the tubules of lower cortex show nearly uniform dilatation and atrophy; in the upper cortex are a few small patches of tubular dilatation; most of the remaining tubules are occluded by the swelling of cells; many casts
78	24	1,900	22	No scars	No bands of contraction; the tubules in the lower half of cortex are uniformly dilated and atrophied; in the upper cortex are groups of dilated tubules surrounded by tubules whose lumina are closed by the swelling of the cells; many casts
109	51	3,270	23	Numerous scars	Several bands of contraction; no tubular atrophy; the cells of the tubules of lower cortex show marked injury
108	49	3,530	21	A few small scars	No chronic changes
109	40	2,600	22	Many old scars producing coarsely granular surface	The outermost portion of the cortex is almost changed to fibrous tissue from which a number of irregular bands run down toward the medulla; in the lower cortex, patches of fibrous tissue are seen; there is irregular scarring of glomeruli and patchy atrophy of tubules; none of these changes can with certainty be attributed to the diet
118	35	1,880	21	Scattered, small scars	Marked uniform atrophy and dilatation of tubules of lower cortex; in the upper cortex, some tubules are atrophied; the others are lined with granular vacuolated cells, some of whole nuclei do not stain; many casts

* Animal accidentally killed while withdrawing blood from heart.

75 per cent. (twelve out of sixteen) of the meat eating rabbits showed such atrophy, whereas it was present in only 9 per cent. (one out of eleven) of the controls.

When it is recalled that the nutrition of the controls because of infection was poor (average individual weight, 1,540 gm.) and that the general condition of the meat fed animals (average individual weight, 2,375 gm.) was excellent, the great difference between 75 per cent. and 9 per cent. becomes the more significant. It seems clear that the infections to which rabbits are naturally susceptible do not frequently cause dilatation and atrophy of the renal tubules. If one adds to this the facts already brought out, namely, that tubular atrophy in control rabbits is but one part of a focal cicatrizing lesion which also causes scarring of the glomeruli and that tubular atrophy in meat eating rabbits is generalized and unaccompanied by fibrosis or by scarred glomeruli, the conclusion that diets containing 27 per cent. or more of protein derived chiefly from meat, when fed for six months or more, are capable of producing high grade dilatation and atrophy of the renal tubules in the rabbit is unavoidable.

Further evidence of the renal injury caused by these high protein diets is obtained from the blood nonprotein nitrogen values.

For control, five adult rabbits were selected at random from the stock cages, fasted twenty-four hours, and blood was then withdrawn from the heart. The following readings were obtained: 29.4, 37.5, 39.0, 46.8, 48.0 mg., with an average of 40.5 mg. These rabbits were then fed the high protein diet for eight days. At the end of this period blood was again withdrawn from the heart, omitting the preliminary fast. The object of this second control was to determine what effect, if any, the high level of nitrogen metabolism would have on the nonprotein nitrogen of the blood. The readings were: 40.2, 43.8, 48.0, 51.6 and 58.2 mg., with an average of 48.3 mg. These data indicated that slight elevations occurring in the animals that had been on the diet for months might be caused by the excessive nitrogen of the diet rather than by an underlying nephropathy, but that considerable increases in the nonprotein nitrogen of the blood must be caused by something other than the high protein metabolism.

In Table 3 will be found all of the blood nonprotein nitrogen readings obtained from rabbits being fed the high protein diets. It is evident that all but one of these animals were retaining nitrogen waste products and that some of them showed high levels of nonprotein nitrogen in the blood. It was impossible to establish any parallelism between the histologic appearance of the kidneys and the degree of nitrogen retention, nor between the latter and the general condition of the animal.

One of the female rabbits being fed on the diet containing 27 per cent. of protein gave birth to a litter of four, sired by a male on the same diet. The observation of these four young rabbits gave further information regarding the injurious effect of the meat-containing diet. The rabbits were born on September 7, when their mother had had the high protein diet for nearly four months. She weaned them on October 10. One of them, weighing 410 gm., died the same day. Necropsy revealed bronchopneumonia. The remaining three took kindly to the high protein diet and gained weight rapidly. Their

TABLE 3.—*Nonprotein Nitrogen of the Blood From Meat Eating Rabbits*

No.	Diet	Duration, Months	Condition of Animal	State of Kidney	Fasting	Blood N.P.N. Mg. per 100 C.c.
88	Protein 27%	4	Good; blood culture negative	Moderate tubular dilatation and atrophy; urine: albumin, few casts	Yes	71
77	Protein 27%	5½	Good; blood culture negative	Tubular atrophy and dilatation; urine: much albumin; many casts	Yes	65
78	Protein 27%	5½	Unable to stand; dying	Extreme tubular dilatation and atrophy; bladder urine: much albumin; many casts	No	124
67	Protein 27%	6½	Unable to stand; diarrhea; blood culture negative	Tubular dilatation and atrophy; bladder urine: much albumin, many casts	Yes	144
61	Protein 27%	7	Good	Tubular dilatation and atrophy; urine: albumin and few casts	Yes	58
108	Protein 27%	11	Excellent	Tubules not atrophied; urine: albumin; no casts	Yes	39
160	Protein 27%	12	Excellent	Tubules not atrophied; urine: no albumin, no casts	Yes	60
60	Protein 27%	7	Good	Tubules not atrophied; urine: albumin; few casts	Yes	60
		11	Purulent nasal discharge; blood culture negative	Urine same	No	79
		13	Excellent	Bladder urine: albumin; rare casts	No	46
147	Protein 30%	5	Excellent	Tubules not atrophied; urine: albumin; some casts	Yes	147
138	Protein 30%	8	Excellent	Tubules not atrophied; urine: albumin; few casts	No	61

general condition, as evidenced by their plumpness, their shiny coats, their bright eyes and their playfulness was excellent and continued so up to the day of death.

The urine of each of these three rabbits was examined on the third day after weaning. All showed albuminuria; one sediment contained many hyaline and granular casts and a few red blood cells. A few casts, but no red blood cells, were seen in the sediments of the other two. The reaction of these urines was tested with phenolphthalein, which remained colorless, and with methyl red, which gave a pale red, indicating that they were nearly neutral.

These rabbits were found dead on October 24, 29 and 31, respectively, when they were from 6 to 7 weeks old. In no case had the general appearance of the animal on the day preceding death indicated that he was in any way different from a healthy young rabbit. Necropsy revealed no abnormalities other than those relating to kidneys.

The kidneys of the animal that died on the 24th weighed 5 gm. (1.1 per cent. of body weight) and on section were found to be pale, wet and totally devoid of markings. No urine was obtained from the bladder.

The kidneys of the animal which died on October 29 weighed 8 gm. (1.6 per cent. of body weight). The section surface was engorged and cloudy, and the cut ends of the vessels stood out as bloody points. The bladder urine contained much albumin, many casts and numerous red blood cells.

The kidneys of the rabbit found dead on October 31 weighed 6.5 gm. (1.6 per cent. of body weight); the surfaces, on section, were pale, moist and lacking in markings. The bladder urine contained much albumin, many casts and red blood cells.

COMMENT

The renal injury which develops in rabbits that are fed a high protein diet may be caused by one or more of a number of abnormal processes:

1. The approximate doubling of the work of the kidney because of the increased nitrogen metabolism comes to mind as such a possibility. But it is well known that normal kidneys merely hypertrophy when required to perform much more than the usual amount of work. Furthermore, one of us reported in a previous paper [4] that simple increase in work brought about by feeding urea to rabbits in amounts sufficient to about double the normal urinary nitrogen for as long as nine months produced no demonstrable renal injury. Simple increase in work does not account for the nephropathy.

2. The excessive ingestion of protein might force its absorption into the blood and the subsequent elimination by the kidney of it or its parenteral digestion products. These substances are believed to be nephrotoxic. This possibility is perhaps emphasized by the work of Longcope,[5] who reported the existence of renal injury in rabbits that had been subjected to anaphylactic shock.

If foreign protein were present in the blood or in the urine, one would expect to be able to demonstrate its presence by means of

4. Newburgh, L. H.: Production of Bright's Disease by Feeding High Protein Diets, Arch. Int. Med. **24**:359-377 (Oct.) 1919.

5. Longcope, W. T.: J. Exper. M. **18**:678, 1913.

biologic reactions. One of us reported in an earlier paper [4] that the plasma of a rabbit whose sole food was boiled egg white contained no precipitin for pure egg albumin, and that neither the albuminous urine nor the blood serum of a similar rabbit was capable of sensitizing guinea-pigs to egg albumin.

This question has been reexamined with the meat containing diet as follows:

Dec. 7, 1922: Some dry powdered beef was shaken in normal salt solution. Two cubic centimeters of the filtrate were then injected intraperitoneally into each of a group of guinea-pigs.

Dec. 20, 1922: The blood serm from two rabbits that had eaten the diet containing beef to the extent of 36 per cent. of protein for weeks, was injected intravenously in 1 c.c. doses each into four of these guinea-pigs. None gave the anaphylactic reaction. One c.c. of a filtrate of the powdered beef was injected intravenously into the remaining three guinea-pigs which had been sensitized to beef protein on Dec. 7, 1922. All showed characteristic anaphylactic shock.

Here also it was impossible to demonstrate the presence in the blood of the protein of the diet. Accordingly, no support was obtained for the surmise that the kidneys were damaged by eliminating foreign protein from the circulation.

The experiments of Longcope [5] dealing with the occurrence of renal lesions in animals that had been subjected to anaphylactic shock have already been mentioned as offering a possible explanation of the question under discussion. He reported the presence of focal lesions in the kidney (and in some other organs). The individual lesion showed various degrees of parenchymatous injury and a well marked infiltration by small round cells. The two most striking features of the lesion were its circumscribed character and the presence in it of many small round cells. There is, accordingly, no resemblance between the focal lesions described by Longcope and the diffuse tubular atrophy reported by us. The great dissimilarity between the two lesions makes it most unlikely that they could have had the same origin.

3. A meat containing diet would, according to current belief, cause the rabbit to secrete an acid urine. Since the rabbit's urine is normally alkaline, such a shift in reaction might be attended by cellular damage. The urines of the rabbits that were eating the beef protein were generally acid to litmus, although not invariably so; a few of them were neutral. It has already been shown in an earlier paper [1] that high protein diets can damage the rabbit's kidney even though the urine remains alkaline. In the experiments referred to, one large group of rabbits was fed soy beans. Even though the urines were always alkaline, the kidneys of animals that had eaten the soy beans for months presented a well marked chronic nephropathy. Another group daily received the following mixture: Casein, 30 gm.; milk,

25 c.c.; scraped carrot, 20 gm.; sodium bicarbonate, 1 gm., and water, 20 c.c. The urines remained alkaline, and the kidneys showed severe parenchymatous lesions.

Polvogt, McCollum and Simmonds [6] have recently published experiments dealing with the nephropathic effect of high protein diets on the kidney of the rat. Their diets were put together in such a way as to make them potentially alkaline and to thus exclude any possible harmful effect resulting from an acid urine. The diets were in addition nearly optimal for growth and reproduction. In spite of these controls, it was found that "all the rats fed the diets high in protein had lesions of the kidneys of considerable severity."

It is evidently not necessary to invoke the acid producing feature of a high protein diet to explain its nephrotoxic character.

Furthermore, it has recently been shown by Hasselmann [7] that the urine of men is less acid when large amounts of meat are eaten than when oats form a considerable portion of the food intake. When the diet consisted of 750 gm. of meat, 100 gm. of fat, 200 gm. of bread, 100 gm. of potatoes and 1,000 c.c. of fluid the titratable acidity was 200 in terms of tenth normal alkali and the hydrogen-ion concentration was 6-7. But when 500 gm. of oats, 100 gm. of fat, 100 gm. of meat, 250 gm. of bread and 750 c.c. of fluid were taken the titratable acidity was 350 and the p_H 5.5.

Hasselmann states that Magnus-Alstleben has pointed out that the urine of the carnivorous dog is not acid but, on the contrary, shows an alkalinity of an order rarely seen in man, and that Loew found that the urine of the rabbit on an oat diet is acid.

We have abundantly confirmed Loew's observation in a group of rabbits that were fed only oats and water for periods ranging from a few months to about ten months; the urines of these rabbits were invariably acid to litmus. Such urines always contained albumin and sometimes casts.

Two of these rabbits lived on oats and water for about ten months. At the end of the first four months the urine of one showed a heavy albuminuria and several casts. The other urine gave positive tests for albumin, but no casts were seen. The urines obtained the day before the rabbits were killed, each showed a well marked albuminuria, and many casts were seen in one sediment but none in the other sediment. The determination (colormetrically) of the hydrogen-ion concentration of these urines gave readings of 5.9 and 5.5.

Necropsy revealed no abnormalities. The kidneys weighed 10.7 gm. and 11 gm. and, except for a few small pits, appeared to be normal.

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6. Polvogt, McCollum and Simmonds: Bull. Johns Hopkins Hosp. **34**:168, 1923.

7. Hasselmann, C. M.: Klin. Wchnschr. **2**:122, 1923.

The microscopic examination of these kidneys revealed no abnormalities except a few casts in the collecting tubules of each kidney.

The urinary abnormalities occurring in the oat fed rabbits might or might not have been caused by the acidity of the urine, since a diet of oats alone produces a metabolic disturbance which also might be attended by a disturbance of the kidney. As long ago as 1916, Lewis and Karr [8] stated that "It is now generally accepted that an exclusive cereal diet results in a failure of normal nutrition for most of the common laboratory animals."

There are at present no data available which make it possible to decide whether urinary acidity alone is capable of causing albuminuria and cylindruria. On the other hand, it is clear that even if acid urine does produce albumin and casts, it does not cause the other changes in the kidney which developed in our meat eating rabbits. The nephropathy which we have found in such rabbits may have been in part, but only in part, caused by the prolonged excretion of an acid urine.

4. The idea that bacterial decomposition of protein in the intestine gives rise to soluble poisons which are absorbed and eliminated by the kidney with injury to it, is familiar to all students of nephritis. And Harvey [9] claims to have produced chronic nephritis by feeding and injecting parahydroxyphenyl-ethylamin. This amin was isolated by Barger [10] from decomposing meat; and said, by Harvey, to have been found in the alimentary canal of man.

The presence of such toxic protein derivatives is said to be indicated by the occurrence of indol in the urine and by an increase in urinary phenol. We have tested the urines of eight rabbits being fed the high protein diet, for the presence of indol with Obermeyer's reagent, and have invariably obtained negative results. In two of these animals the twenty-four hour excretion of phenol in the urine was quantitated by the method of Folin and Denis.[11] Our figures were somewhat lower than those obtained by Folin and Denis from normal rabbits.

We, accordingly, obtained no evidence of the excretion of abnormal amounts of bacterial decomposition products. While our examination was inadequate to exclude entirely such a possibility, it left us in the position of having no data which indicated that the disease of the kidney was attributable to the damaging effect of such substances.

5. Levene and Van Slyke,[12] in 1912 showed that amino acids are always present in normal urine, and that the total amino acid nitrogen

8. Lewis, H. B., and Karr, W. G.: J. Biol. Chem. **28**:17, 1916.
9. Harvey, W. H.: J. Path. & Bacteriol. **16**:95, 1911-1912.
10. Barger: J. Physiol. **38**:343, 1909.
11. Folin and Denis: J. Biol. Chem. **22**:319, 1915.
12. Levene and Van Slyke: J. Biol. Chem. **12**:301, 1912.

bears a fairly constant relation to the total urinary nitrogen. Van Slyke [13] in a subsequent paper reported that during the digestion of meat the amino acid content of the dog's blood is markedly increased. More recently Folin and Berglund [14] have published tables which make it clear that there is an increased elimination of amino acids by the kidneys of man whenever there is an influx of amino acids from the digestive tract sufficient to raise materially the amino acid content of the blood. The greatest elimination of amino acid occurred in a subject who took 135 gm. of gelatin. Before eating the gelatin, the blood contained 5.5 mg. of amino acid nitrogen per 100 c.c., and the kidney was putting out 10 mg. of amino acid nitrogen an hour. Two hours later, the blood amino acid nitrogen had risen to 11 mg. per 100 c.c., and the kidney during the fourth hour following the ingestion of the gelatin put out 96 mg. of amino acid nitrogen.

It is conceivable that the increased elimination of amino acid which follows the excessive ingestion of protein might not be without effect on the kidneys. Some of the amino acids might be nephrotoxic when excreted in unusually large amounts for a long time.

Experiments [15] designed to throw some light on this question have progressed far enough to permit a preliminary statement. The intravenous injection of an amino acid is regularly followed by a sharp increase in the urinary amino acid. The injection of a number of the straight chain amino acids in large amounts has caused no demonstrable injury to the kidney. But the intravenous injection of tyrosin and of histidin in very much smaller doses has been regularly followed by the occurrence and often persistence for a number of days of albumin and casts.

These results, while suggestive, are not sufficient to make us willing to affirm that high protein diets cause renal damage because they are attended by the excretion of nephrotoxic amino acids.

6. The question whether the renal injury was caused by intercurrent infection has already been discussed, and ample evidence has been presented to show that the naturally occurring infections of rabbits do not produce the type of kidney disease which was found in the meat eating animals. On the other hand, it is possible that the high protein diet produced a primary renal injury that made the kidneys accessible to the harmful effects of bacteria, which in the absence of such a primary lesion were incapable of causing the lesion. Even though the necropsies did not give us the usual evidence of infection, and even though every blood culture was negative, it is true that infection could not with certainty be excluded. It is accordingly impossible to state whether bacteria were in part responsible

13. Van Slyke: J. Biol. Chem. **12**:399, 1912.
14. Folin and Berglund: J. Biol. Chem. **51**:413, 1922.
15. Newburgh and Marsh: To be published.

for the final picture. We are, however, convinced that the primary injury was a product of the diet, and that if bacteria played any part in causing the lesion they were able to do so only as a result of damage previously worked by the diet.

SUMMARY

The majority of rabbits that ate a diet containing 27 per cent. or more of protein for six or more months, developed a chronic nephropathy. At least the initial lesion was caused by the products of the diet, since spontaneous infection in the absence of the diet is incapable of causing the disease. The lesion may, in part, have been caused by infection acting on a kidney made susceptible to infection by the diet.

The evidence at hand suggests that the injury caused by the diet is either solely attributable to the excessive excretion of some amino acids or in part to the amino acids and in part to the acid character of the urine. But the acidity of the urine by itself is incapable of causing all of the injury attributable to the diet.

There is no intention on our part of claiming that this nephropathy is the anatomic analogue of human chronic nephritis. On the other hand, the recent work of Polvogt, McCollum and Simmonds [6] "furnishes experimental evidence that the excretion of excessive amounts of the normal end products of protein metabolism may result in anatomical damage to the kidneys of an omnivorous animal when all other requirements for the nutrition of this species are adequately provided for." Furthermore, Squier and Newburgh [16] have published data which, in their opinion, prove that the human kidney may be injured by protein excess. The authors of this paper believe that these experiments on the rabbit bring us one step nearer to an understanding of the etiology of chronic nephritis in man.

16. Squier and Newburgh: Renal Irritation in Man from High Protein Diet, Arch. Int. Med. **28**:1 (July) 1921.

PERIARTERITIS ACUTA NODOSA*

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About seventy observations of periarteritis nodosa have been recorded in medical literature. The disease is still so obscure however that every new case reported may assist in its final elucidation. I shall discuss briefly a case observed in the Stanford Medical Service at the San Francisco Hospital.

REPORT OF A CASE

History.—I. G., a Persian janitor, aged 38, was admitted to the San Francisco Hospital on Dec. 12, 1922, complaining of severe pain in the stomach one or two hours after eating, without local tenderness, followed frequently by eructations of gas; also of occasional night sweats. These symptoms had commenced in July, 1922. One week after the onset of these symptoms his appendix had been removed, which gave him temporary relief. He remained at the hospital for about ten days. The pain in his stomach returned, however, and persisted at varying intervals until his entrance to the San Francisco Hospital five months later. He was nauseated at times but had never vomited. Recently he had had nocturia three or four times. The patient did not speak English very well, and for that reason it was difficult to obtain an accurate history, but so far as could be made out, he had always been well until the appearance of these symptoms. He denied venereal and other severe infections. He had been injured several times during the Great War, but not severely. He did not use liquor or tobacco. He had been married for eighteen years. He had three children, all of them well, the oldest one being 17. He had lived in Persia until six years ago when he came to the United States. His average weight had been 150 pounds (68 kg.), but since he had been ill he had lost weight until his weight at entrance to the hospital was 115 pounds (52.1 kg.).

Physical Examination.—The patient was undernourished. He coughed occasionally without raising any sputum. His pupils were slightly irregular and reacted fairly well to light and accommodation. There was a subconjunctival hemorrhage in his right eye. His tonsils were moderately enlarged, and in the crypts there was some grumous material. Examination of the lungs did not reveal anything abnormal. The heart seemed to be within normal limits. The heart sounds were loud and snapping; the second pulmonic tone was greatly accentuated and rough. No definite murmurs were heard. A careful examination of the abdomen did not reveal any abnormalities. There was no spasticity or tenderness anywhere. There were no paralyses. The patient did not complain of any abnormal sensations. The patellar reflex was sluggish, especially on the right side. Two blisters were found in the skin on the inner side of the right knee.

A fluoroscopic examination revealed considerable grayness at both apexes and fixation of the left diaphragm. A careful examination of the nose by a specialist revealed some irregularity of the septum, a good breathing space and no discharge. Urinalysis revealed little albumin and occasional hyaline and granular

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casts. The hemoglobin content of his blood was 70 per cent. There were 4,000,000 red blood corpuscles and 6,300 white cells. A month later the leukocyte count rose to 11,350. The differential count was normal at all times. There was no eosinophilia. The blood Wassermann reaction was negative. His blood pressure was: systolic, 100; diastolic, 80. A blood culture showed streptococci in one bottle, the other bottle remained sterile. Analysis of the stomach contents showed a slight increase in free hydrochloric acid, but the stomach contents were otherwise normal.

Treatment and Course.—The patient was placed on a soft diet, which caused some improvement in his gastric symptoms.

On January 23, dulness was noticed at both bases with bubbling râles. There were a few wheezing râles over both apexes. The liver was not palpable. A general enlargement of the lymph glands was also noted, and the patellar reflexes were still more sluggish. On the whole, he had improved somewhat and was able to get up, but he was never quite well.

On January 26, he said that he had passed bright blood in his stools during the night. Examination at this time showed a puffy swelling on the right side of his face, and also some difficulty in breathing, the breathing being of an asthmatic character. All through the chest there were numerous musical râles. The heart sounds were clear and rapid. On this day, a definite enlargement of the liver was discovered, the lower border of the liver being 5 fingerbreadths below the costal margin.

On January 27, roentgen-ray examination revealed fluid in both pleural cavities, the heart at the upper limit of normal size, and there was a marked enlargement of the liver. On account of evident cardiac insufficiency he was given digitalis in large doses, after which his pulse became somewhat irregular and extrasystoles developed.

On January 31, the patient was much worse; his breathing was labored; there was impaired resonance throughout his chest and marked flatness at both bases. There were many extrasystoles. An accumulation of fluid could be made out in the abdomen and his liver remained markedly enlarged.

On the next day, February 1, the fluid had increased in both pleurae and in the abdomen. On this day there was a slight rise in temperature.

On February 4, a slight edema of the lower extremities was observed. His pulse was distinctly irregular, and edema of the right lower eyelid had developed.

On February 5, weakness was noticed in the seventh cranial nerve on the right side and ptosis of the left eyelid. The signs of cardiac decompensation continued.

There was a short period of improvement from February 7 to February 12, and on February 12 his pulse was regular, slow and of low tension.

On February 18, the accumulation of fluid in his pleural cavities had apparently disappeared.

On February 22, he developed edema of the right hand and of both feet. His pulse was 100, regular.

On February 28, he was again in marked distress with dyspnea, wheezing respiration and much sweating.

On March 1, he was much worse, his pulse was very rapid, there were many extrasystoles, and his respiratory distress was pronounced.

He died quietly on March 2 at 3:30 a. m.

During the course of his illness at the hospital his temperature was normal or subnormal with an occasional rise to 100 F. There was much sweating, especially during the periods of exacerbation of his illness. The pulse rate ranged between 70 and 110, but was usually high. The respiration rate varied between 20 and 30. Urinalysis from time to time showed a small amount of albumin and a few hyaline and granular casts. His blood pressure was consistently low. The fluid removed from his chest contained much albumin, a considerable number of leukocytes, mostly polymorphonuclears (about 70 per

cent.). No eosinophils were noted. On February 1, some diplococci were noticed in a smear from the pleural fluid, but a culture made at the same time did not show any growth. His sputum, of which there was little, was examined several times for tubercle bacilli, always with a negative result.

The findings and the course of the disease were so unusual that the clinicians refused to make a diagnosis.

Necropsy.—Necropsy was performed on March 2, 1923. The body was that of a strongly built, fairly well nourished and muscular man of about 40 years. His pupils were widely dilated and equal. The face and neck showed marked cyanosis. The left axillary and the femoral lymph glands on both sides were distinctly enlarged. Many purple spots from 2 to 10 mm. in diameter were seen in the skin on the inside of the left thigh. Both legs showed a moderate edema. A scar was found in front of the right tibia, which was moderately firmly attached to the bone (healed war wound). Two small pigmented halos were seen in the skin on the inside of the right knee. The scrotum was slightly edematous. The finger tips were cyanotic. The veins about the anus were markedly dilated. The complexion was very dark (Persian). The skin was dark all over the body.

A scar from a healed laparotomy was seen on the right side in the appendicial region (appendectomy). A recent small superficial incision was found in the midline about half way between the umbilicus and the pubic region.

The abdomen was distended and tense with gas. The omentum was slightly adherent to the anterior abdominal wall. The subcutaneous fat was atrophied. The abdominal muscles were pale and poorly developed.

The liver projected 4 fingerbreadths in the right mammillary line and in the left lobe 5 fingerbreadths below the xyphoid process.

The lower border of the stomach was at the umbilicus.

The omentum showed some small irregular scars.

The peritoneum showed a dark purplish discoloration. It was smooth, glistening and moist; 50 c.c. of blood stained fluid were found in the rectovesical pouch.

The level of the diaphragm on the left side was at the fourth rib, on the right side at the fifth rib.

The chest was strongly arched, almost barrel shaped, and symmetric.

A few easily broken adhesions were found in the lower part of the left pleura. About 100 c.c. of clear fluid were present at the left base. Few easily broken adhesions were noticed in the upper part of the right pleura, and about 150 c.c. of clear fluid in the lower part.

In the pericardium there were 200 c.c. of slightly turbid yellow fluid. Both layers of the pericardium were irregularly congested and covered with a thin layer of fibrin. In the inflamed pericardium at the base of the heart there were some just visible grayish nodules. A large milk spot was found over the right ventricle.

The heart was slightly enlarged. The right side was dilated. Dark fluid blood filled the pulmonary artery. The right ventricle and the right auricle were distinctly dilated. The wall of the right ventricle was firm, measuring 4 mm. on cross-section. Many just visible grayish nodules were seen in the pericardium over the pulmonary artery. The pericardium along the course of the coronaries and their branches were rather white and thick, but there were no nodules at these points. The left ventricle was not dilated. It measured 12 mm. on cross-section. The base of the aorta and the coronary arteries were normal. The heart muscle on the left side was firm and full of grayish white, small irregular spots. The valves of the heart were normal.

A large amount of mucopurulent material was found in the left bronchus. The left pleura was smooth and glistening. The left lung was large and emphysematous. The bronchial tubes were congested. The bronchi in the lower lobe contained much mucopurulent material. The peribronchial lymph nodes were enlarged, moist and contained a few grayish spots. The posterior lower parts of the left lung were congested and edematous.

The right peribronchial lymph glands were large. Many grayish white nodules were seen in the pleura at the right apex. There was also present a superficial scar 1.5 cm. in diameter. The right lung otherwise resembled the left one. The tissue at both bases was quite firm.

A few old adhesions were found about the spleen. Its capsule was slightly thickened. The splenic artery was normal. The spleen measured 13.5 by 8.5 by 4 cm. The markings were distinct.

The left suprarenal body was small, otherwise normal.

The left kidney was large. The capsule stripped easily. It measured 15 by 6 by 3.5 cm. The cortex was dark purple and showed a large number of grayish white opaque spots. On the cut surface the cortex was quite wide and full of similar spots. The pyramids showed a marked passive congestion.

The right suprarenal was like the left one. The right kidney was similar to the left one.

The bladder, the prostate, the seminal vesicles and the rectum were normal.

Easily broken adhesions were found in the region of the gallbladder, extending quite a distance into the surrounding area. The duodenum and its contents were normal. The bile duct was patent.

The stomach was much distended. It contained grayish fluid and many flakes of mucus. Some adhesions were present between the stomach and pancreas. The mucous membrane of the stomach was somewhat congested. It was covered with a thick layer of mucus. The fundus showed postmortem digestion.

The lymph glands at the liver hilus were enlarged and smooth. Their cut surface was dark red.

The pancreas was normal.

The abdominal arteries were normal.

The gallbladder was filled with thick viscid bile.

The liver measured 28 by 24 by 9 cm. In and underneath the capsule there were irregular white strands apparently following the course of the larger blood vessels. The cut surface showed an extreme passive congestion and a definite thickening of the connective tissue about the larger blood vessels. There was also a marked cyanosis of the centers of the lobules and evidence of beginning cyanotic atrophy.

The appendix had been removed. No adhesions were seen at the point of operation.

No intestinal parasites were found. The mucous membrane of the lower ileum and of the large intestine showed a marked passive congestion. It was otherwise normal. The mesenteric lymph glands were slightly enlarged, congested and grayish red. The retroperitoneal glands were in the same condition. No signs of tuberculosis were discovered in them.

The thoracic and abdominal aorta was normal.

The skull was distinctly asymmetric, the skull cap being flatter in the right occipital region. It was otherwise normal. The longitudinal sinus contained fluid blood. The pia mater on both sides was slightly congested. The brain showed an asymmetry similar to that of the skull. The large arteries at the base of the brain were normal. The large venous sinuses were normal. There were no visible lesions in the motor cortex. The brain tissue was hyperemic and edematous throughout. No focal lesions were found.

Anatomic Diagnosis.—The anatomic diagnosis was: (1) acute nodular periarteritis, (2) subacute myocarditis of the left ventricle with hypertrophy and dilatation of the right ventricle, (3) emphysema, (4) healed apical tuberculosis of the lungs, (5) subacute nodular pericarditis, (6) subacute pleurisy, (7) subacute peritonitis, (8) subacute nephritis and (9) healed appendectomy.

Histological Examination.—Sections of the lung showed an involvement of the small arteries, of the veins, of the pleura and the interlobular septums, of the bronchial tubes and of the pulmonary tissue proper. The lesions in the small

arteries (Fig. 1) consisted in a heavy infiltration of the peripheral layers of the adventitia with leukocytes, mostly with eosinophils, but there were also a few lymphocytes and plasma cells. In the central parts of the adventitia the leukocytes were much less numerous. Here there were mostly fusiform or irregularly shaped cells which contained large clear nuclei. The general appearance of these cells was that of fibroblasts. The muscular layer was generally fairly well preserved, but there were places in which the muscle cells were more or less vacuolated and in which the media was invaded both by the eosinophils and the large proliferating cells of the adventitia. The changes in the adventitia were not localized in the shape of nodules but were quite diffuse, although there were stretches of the small arteries which were quite normal. There were marked changes in the intima consisting of a marked cellular thickening of this coat apparently corresponding more or less closely to the damaged parts of the media. The cells in the intima also had the characteristics of fibroblasts, and there were delicate fibrils between them. Where the process was recent

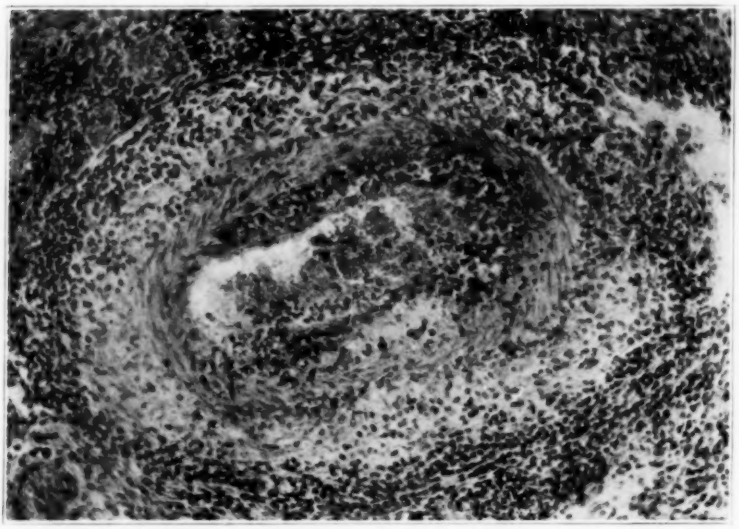

Fig. 1.—Small branch of pulmonary artery showing lesions of periarteritis.

some of these cells may have been derived from the endothelium. In the thickened intima there were few eosinophils which seemed to come from the adventitia. In some places (Fig. 2) the intima contained some homogeneous material which stained a bright red with eosin (evidently coagulated plasma, as was shown by irregular masses of fibrin in it). It was present in narrow bands, but sometimes it occurred in large quantities practically occluding the lumen. It could be demonstrated, however, in most places that this material was still underneath the endothelium. The material contained more or less degenerated leukocytes. Even where the lumen was much narrowed it was still free and filled with normal blood. In other vessels there was evidence of recent thrombosis. The intimal changes were not so diffuse as those in the adventitia, but they also were not distinctly nodular. The media even at the most severely altered places remained fairly intact. There was no evidence of aneurysmic dilatation of any of the affected arteries.

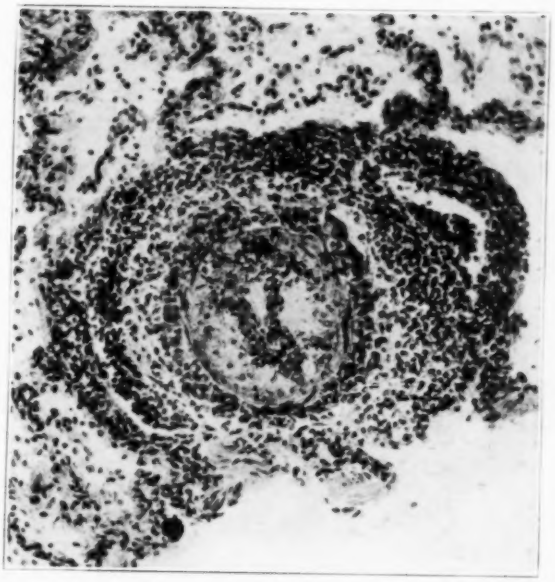

Fig. 2.—Smaller branch of pulmonary artery showing more acute changes, with coagulated exudate in intima.

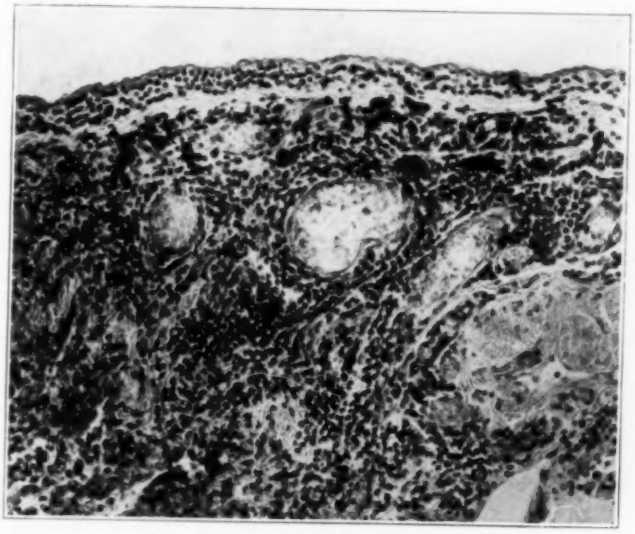

Fig. 3.—Section of pleura with marked subacute pleurisy.

Many of the small veins showed a heavy infiltration of their adventitia with leukocytes (mostly eosinophils). In a few of them the endothelium was distinctly swollen and evidently proliferating.

The perivascular lymphatics were distended with leukocytes, mostly eosinophils.

The large arteries and large veins were normal, but some of them contained recent thrombus.

The pleura (Fig. 3) and interlobular septums were heavily infiltrated with eosinophil leukocytes, and the blood vessels in them were very much congested. Where the endothelial layer of the pleura was still preserved, the endothelial cells were distinctly swollen. On the surface and between the endothelial cells there were many diplococci in most places, although some were free from

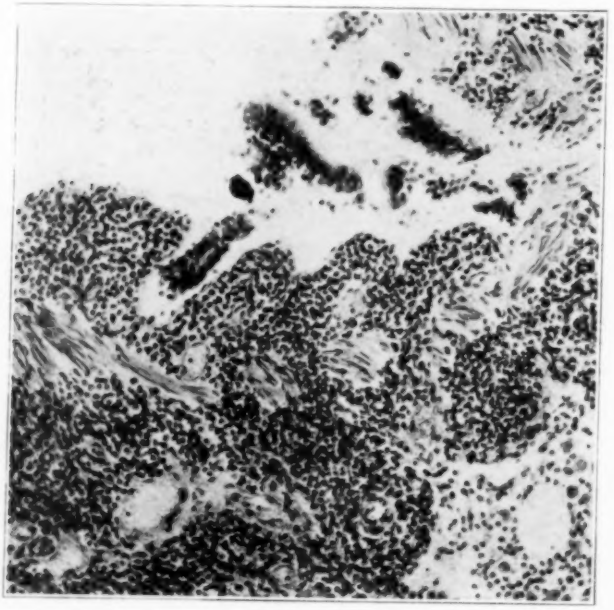

Fig. 4.—Section of bronchus with tremendous infiltration of mucous membrane with eosinophils.

them (contaminations). There were no deposits on the surface of the pleura. The top layer of the pleura was sometimes excessively infiltrated with leukocytes. The lesions in the pleura were quite diffuse and had no direct relation to the blood vessels.

The wall of the bronchi (Fig. 4) were diffusely and heavily infiltrated with eosinophils. There were also a few lymphocytes and some fibroblasts. The change was most marked in the mucous membrane and in the loose peribronchial connective tissue. It seemed to extend diffusely from the largest bronchi down to the respiratory bronchioles. Some of the bronchial arteries show marked periarteritis and endarteritis with partial destruction of the media.

The pulmonary tissue proper (Fig. 5) showed a diffuse infiltration with eosinophils. This in places led to the formation of small areas of broncho-

pneumonic consolidation in which the air spaces were filled with eosinophils, large mononuclear cells, lymphocytes and red blood corpuscles. The air spaces in these areas contained considerable fibrin. Even in such places no bacteria could be demonstrated.

Section of a peribronchial lymph gland contained a moderate amount of coal pigment. The cells in the proliferative centers were swollen and more or less degenerated. The centers contained a few neutrophilic leukocytes and in the periphery deposits of fibrin, some of which were quite hyaline. The lymph spaces were dilated and filled with red blood corpuscles, many eosinophils, a few lymphocytes and large mononuclear cells. The lymph-adenoid tissue was full of plasma cells and was diffusely infiltrated with eosinophils. The capsule showed perivascular infiltrations with eosinophils and plasma cells which extended into the loose connective tissue on the outside. A larger artery

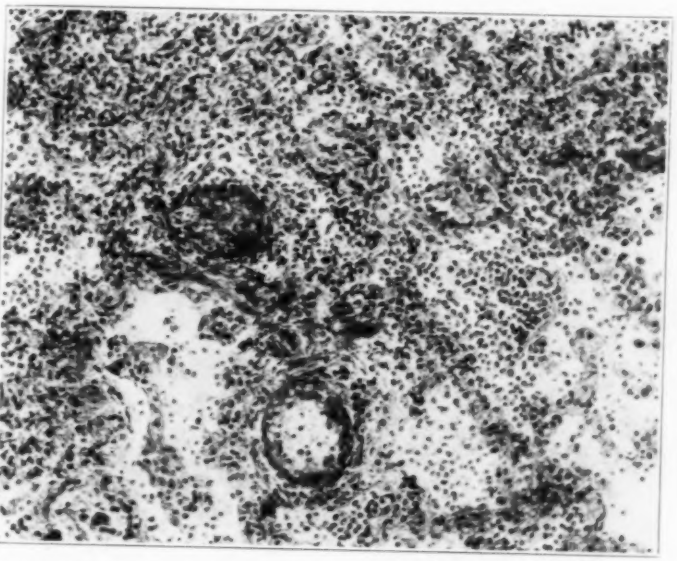

Fig. 5.—Two arterioles in lung occluded by disease and inflammatory infiltration of pulmonary tissue.

near the lymph gland showed characteristic lesions: infiltration with plasma cells and eosinophils in the peripheral adventitia, proliferation of connective tissue in the central adventitia with invasion of the damaged media, marked cellular thickening of the intima with moderate infiltration with eosinophils, swelling, partial detachment and proliferation of endothelial cells with a collection of leukocytes and red cells underneath the partly detached endothelium, infiltration of the intima with uncoagulated plasma and fibrin.

Other lymph glands showed similar lesions. The large lymphatic vessels near them were distended with lymph in which there were many eosinophils, fewer lymphocytes and plasma cells and few neutrophilic leukocytes.

The pulp of the spleen was diffusely infiltrated with eosinophilic leukocytes; the proliferative centers in the malpighian bodies showed the same lesions as those in the ones of the lymph glands. The arterial lesions were not marked.

The adventitia of a few small arteries was thickened and fibrous, and there were a few eosinophils in the new fibrous tissue. The media and the intima of these arteries were of normal appearance. A small amount of hematogenous pigment was found in the pulp.

Some of the larger arteries of the heart showed characteristic changes: heavy infiltration of the adventitia with eosinophils, lymphocytes and plasma cells, cellular proliferation of inner parts of adventitia with often deep invasion of the not severely damaged muscle by cellular new connective tissue with many capillaries in which there were many leukocytes, infiltration of the intima with eosinophils and cellular proliferation, swelling and partial detachment of the endothelium. Similar lesions were also found in the walls of some of the veins. The perivascular connective tissue all through the heart muscle was heavily infiltrated with leukocytes and showed a marked cellular proliferation, and from there the process extended quite diffusely into

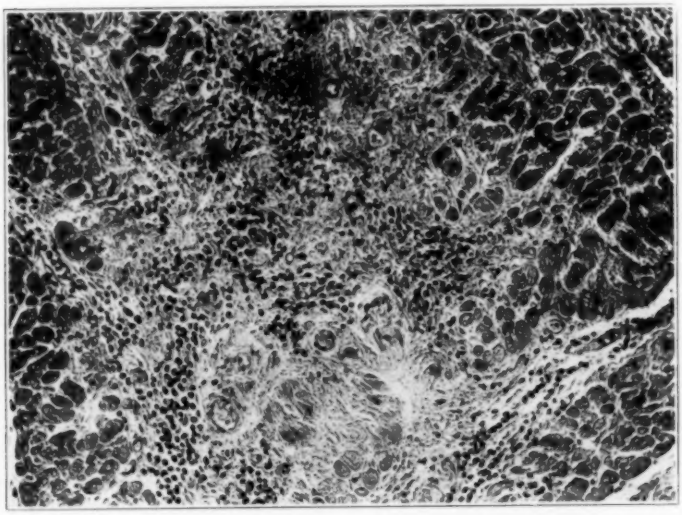

Fig. 6.—Marked subacute interstitial myocarditis.

the musculature (Fig. 6). This was especially noticeable on the right side. Here there were even considerable collections of eosinophils and lymphocytic cells between the muscle and the endocardium. In the diseased muscle there were some fairly large cellular scars. The most remarkable lesions were found in the pericardium (Fig. 7) where, in addition to the characteristic changes in many arteries and some veins, there was a diffuse infiltration of the fat with leukocytes and a nodular proliferation of the top layers which was especially marked on the right side. These nodules arose from the connective tissue of the surface layer of the pericardium with a broad base, and projected over the surface. They were of about the size of tubercles, and consisted of vascular young connective tissue full of eosinophils and plasma cells. Their surface was covered with swollen endothelium, and in them were numerous small glandlike crypts lined with cuboid endothelial cells. The endothelial cells on the surface of the pericardium were swollen everywhere. In some places the surface was contaminated with bacteria of various kinds, but otherwise no bacteria could be found in the sections.

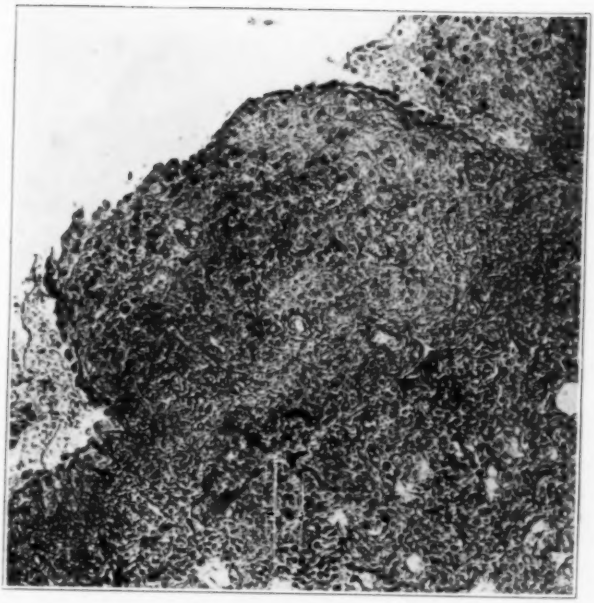

Fig. 7.—Nodular subacute pericarditis.

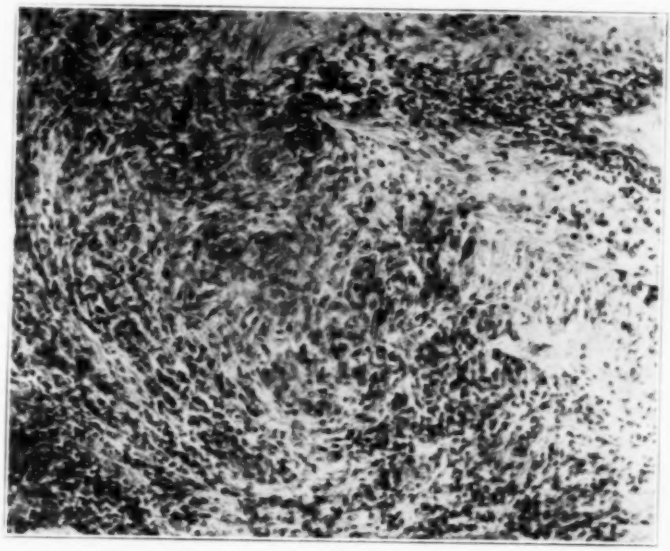

Fig. 8.—Granulomatous nodule in branch of renal artery with destruction of media.

In an artery of medium size the muscle cells in some places were more or less vacuolated; the intima showed a cellular thickening and contained a moderate number of eosinophils. The arterioles in the surrounding fat showed a marked infiltration of the wall, with large fibroblasts with nearly complete obliteration of the lumen. The latter lesions were somewhat nodular in character.

The changes in the medium sized arteries of the kidney were severe (Fig. 8); the infiltration of the adventitia with eosinophils and lymphocytic cells was marked, the proliferation of the inner layer pronounced; the muscle was actually necrotic and hyaline in a few spots, in others distinctly vacuolated and in places completely destroyed by the invasion of granulation tissue from the adventitia. The intima contained some eosinophils and showed a marked cellular proliferation; the endothelium was swollen. In some places the

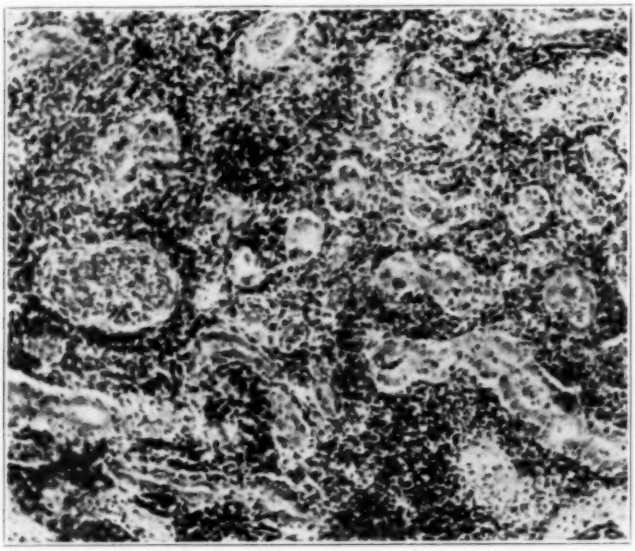

Fig. 9.—Diffuse subacute interstitial nephritis.

thickened intima was full of hyaline material. The connective tissue proliferation which arose from the adventitia in some places was distinctly nodular. The nodules were cellular, contained blood vessels, were about the size of tubercles and lay partly in the inner layer of the adventitia, partly in the destroyed media. The nodules consisted of unusually large fibroblasts and contained some eosinophils and lymphocytic cells. None of them showed evidence of caseation. The endothelial cells of the blood vessels were often very much swollen, but no giant cells were found. In some of the small arteries the wall was entirely destroyed by the granulation tissue, the lumen was closed, or new lumina had been established by capillary dilatation in the new connective tissue. From the perivascular connective tissue granulation tissue heavily infiltrated with eosinophils and plasma cells radiated far out into the kidney tissue proper (Fig. 9), filling the spaces between the tubules and causing their collapse. In the tubules in these areas one often found accumulations of more or less degenerated eosinophils or hyaline casts. The epithelial

cells of the convoluted tubules were swollen and partly desquamated; in places they had formed large multinuclear giant cells by fusion. The glomeruli were congested, but even in the areas with interstitial inflammation they were otherwise normal. Many of the small veins were surrounded by heavy masses of leukocytes. The arterioles did not seem to participate in the process. The infiltration with eosinophils and lymphocytic cells in places extended far down into the pyramids. No bacteria were found in the section in spite of careful search.

The lesions in the arteries of the liver (Fig. 10) were practically identical with those in the kidney. The destruction of the arterial wall was often even more complete, the tendency of the granulation tissue to arrange itself into cellular nodules even more marked. The tendency to proliferation of the vascular endothelium in these nodules was also pronounced. In the center

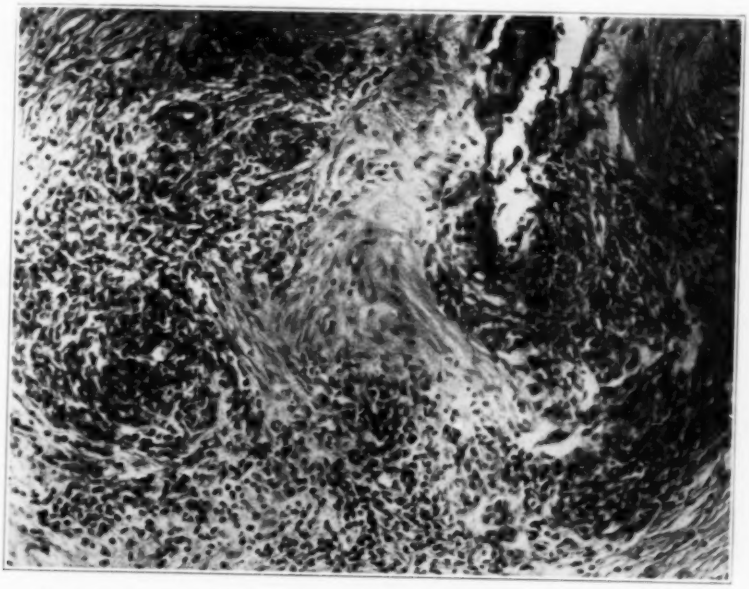

Fig. 10.—Several granulomatous nodules in wall of branch of hepatic artery.

of some of the obliterated arteries new lumina had developed from the dilated capillaries. In the proliferating connective tissue there were many eosinophils, and in some places coagulated fluid was seen. The perivascular connective tissue was heavily infiltrated with eosinophils and plasma cells and often greatly thickened, but there was little evidence of an invasion of the liver tissue proper. The liver cells were normal, except that the central capillaries were greatly dilated and the liver cells between them distinctly atrophied. In the capsule of the liver some of the small arteries were distinctly diseased, and there was a moderate diffuse infiltration with eosinophils and plasma cells. No nodules were seen. In these sections also no bacteria were discovered.

In the pancreas some of the larger arteries were badly diseased, resembling very much those found in the heart. There was a moderate infiltration of the interlobular connective tissue with eosinophils and plasma cells and a similar quite heavy infiltration about some of the ducts. Even between the acini and

in the islands of Langerhans eosinophils were found singly or in groups. The glandular tissue was otherwise quite normal. No bacteria were found in these sections.

The prostatic glands contained many amylaceous bodies. They were otherwise normal. In the prostate, and especially in the muscle surrounding it in the periphery, there were many large irregular areas of infiltration with lymphocytes, plasma cells and eosinophils. Some of the arteries showed a complete replacement of the wall with dense rather cellular fibrous tissue with almost complete obliteration of the lumen. The endothelial cells were swollen. In the peripheral parts of the adventitia there were many eosinophils. A sympathetic ganglion near these blood vessels was diffusely infiltrated with eosinophils. A small vein was also surrounded by numerous eosinophilic leukocytes.

The mucous membrane of the stomach was moderately but diffusely infiltrated with lymphocytes, plasma cells and eosinophilic leukocytes. The glands were normal. In the submucosa many eosinophils were found in the immediate vicinity of both arteries and veins, but the vessels themselves were not altered. The connective tissue between the bundles of the muscularis and about the blood vessels of the muscular coat was also full of eosinophils. The blood vessels themselves were normal, except a few larger arteries which show marked changes. Similarly the peritoneum contained some eosinophils, and in one place there was a small projecting vascular nodule full of eosinophils.

The lesions in the mucosa, submucosa, muscle and peritoneum of the small intestine were very much like those in the stomach. The peritoneum was more seriously involved; there were more lymphocytes and plasma cells, and the vascular nodules on the surface were more numerous. The peritoneal endothelium was not preserved.

The eosinophils in the mucous membrane of the colon were quite numerous. There was little change in the submucosa. In the muscle and in the peritoneal tissue arteries were found in which cellular fibrous tissue had developed both in the adventitia and the intima, accompanied by the usual infiltration with leukocytes.

Many muscle fibers of the abdominal musculature showed evidence of waxy (hyaline) degeneration; the endomysium and perimysium were moderately infiltrated with eosinophils. In few small arteries the walls were replaced by cellar fibrous tissue, and the lumina were practically obliterated. In the intermuscular fat there were many eosinophilic leukocytes and some lymphocytes.

The brain tissue and the blood vessels in it and in the pia were normal except for the presence of a few lymphocytes in the perivascular lymphatics here and there.

Bacteriologic Examination.—Smears from the pericardium stained with Grain stain or Giemsa stain showed many red blood corpuscles, many endothelial cells, many small and large lymphocytes, few polymorphonuclear neutrophilic leukocytes, some large phagocytes containing degenerated red cells and coarse brown pigment granules and a few uncertain diplococci. No other bacteria were found. Smears from the spleen showed normal cells, no bacteria. Smears from the bone marrow showed many eosinophilic myelocytes, otherwise normal cells. No bacteria were found. Smears from the left renal pelvis showed many epithelial cells, few leukocytes, no bacteria.

Rabbit 5 was inoculated in the right testicle, the right ear and intraperitoneally with mixed scrapings from the liver and kidney lesions in beef tea on March 5, 1923.

Guinea-pig 6 was inoculated into the right testicle, subcutaneous tissue on the belly and intraperitoneally with the same material on March 5, 1923. Guinea-pig 6 died on March 7, 1923, at noon. Necropsy, on March 7, 1923, 5 p. m., revealed: a distended belly, an injected peritoneum, an intestine distended with gas, very little serous exudate. The right testicle was swollen and congested. Smears of the peritoneum showed a few red blood corpuscles a

few polymorphonuclear leukocytes, many small gram-positive diplococci and short chains and a few other bacteria. The stomach at necropsy was found perforated as a result of postmortem digestion. Cultures from the peritoneum on slant agar and beef tea did not show any growth.

A smear of a testicle showed many large poorly staining cells, few lymphocytes and few polymorphonuclear leukocytes; no bacteria were found in spite of careful search. Cultures on the same mediums did not show any growth.

Smears stained with Giemsa showed the same results; no spirochetes or other parasites were seen in any of the smears in spite of good stain and brilliant illumination.

Rabbit 5 was killed on May 8, 1923. No gross lesions were discovered at necropsy, except a moderate probably spontaneous cirrhosis of the liver. Sections from various organs did not reveal any characteristic lesions. In the liver the periportal connective tissue showed a marked round cell infiltration, which naturally led to some round cell infiltration of the wall of the blood vessels in it. Similarly some of the blood vessels in the lungs showed a few lymphocytic cells in the adventitia, but the changes were so little characteristic that the result must be considered negative. Cultures of the tissues of the rabbit were made on a great variety of mediums, with negative results.

Fig. 11.—Small silver precipitates in cells of inner adventitia of diseased artery. High power magnification.

Several rabbits were injected intravenously with the fluid obtained from aseptically ground up organs filtered and unfiltered, but they promptly died, probably of fibrin ferment poisoning. Two more injected intraperitoneally with filtered and unfiltered tissue fluid did not develop any lesions.

Sections from practically all organs in this case were stained with the Giemsa stain and carefully searched for bacteria, with negative results except for the contaminations noted in the protocols of the histologic examination.

Pieces from lungs and pleura, the spleen, the liver, the kidneys, the heart and pericardium were stained according to the Levaditi method. No spirochetes could be detected in them in spite of careful search. In the cell bodies of the proliferating cells in the inner layer of the adventitia in various organs minute silver deposits were found in the shape of small round or slightly rod shaped objects, which are shown in Figure 11. Whether they have any particular significance could not be determined. It might be well to look for them in future cases. They occur in the place that is suspected by many to harbor the initial infection, but silver deposits in impregnated specimens are notoriously misleading.

SPECIAL FEATURES IN AUTHOR'S CASE

1. The almost complete absence of any gross nodules in connection with the disease of the arteries and the complete absence of the development of aneurysms. This, however, has also been noticed in other early cases.[1] The lack of aneurysms in this case is probably to be explained by the comparative absence of extensive medial destruction and the massive development of fibrous tissue in those places in which the media is completely destroyed. Microscopic granulomatous nodules in the inner adventitia extending into the media with destruction of the latter were found in the sections of kidney and liver.

2. The marked involvement of the serous membranes with development of just visible granulomatous nodules on the surface of pericardium and peritoneum. The occurrence of pleurisy, pericarditis and peritonitis in connection with the disease is mentioned in several cases in the literature; the latter, however, was usually due to perforation of intestinal ulcers. The granulomatous nodules I have not found mentioned in any report except in a recent one of Fishberg,[2] who describes in his case in the pericardium flat white thickenings and fine nodules without, however, giving a more detailed description of them.

3. The diffuse infiltration of the bronchial tubes with eosinophilic leukocytes similar to that which is commonly observed in asthma, with asthmatic symptoms. This seems to be an unusual occurrence in periarteritis nodosa. Lamb[3] reports that in one of his cases the patient had suffered from asthma of increasing severity, but this is the only reference to this condition which I have been able to discover.

4. The extensive involvement of the smaller branches of the pulmonary artery. The bronchial arteries have been found diseased in quite a few cases, but the pulmonary arteries rarely[4] (in Walter's case the lesions were purely microscopic).

5. The infiltration of the pulmonary tissue itself with the development of small pneumonic foci full of eosinophils in which no bacteria could be demonstrated. Mönckeberg[5] is the only one who describes similar lesions of the lung.

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1. Hart: Ueber Mesoperiarteriitis (Periarteriitis nodosa), Berl. klin. Wchnschr. **45**:1305, 1908. Künne über Mesoperiarteriitis (Periarteriitis nodosa), Frankfurt. Ztschr. f. Path. **5**:105, 1910. Fishberg: Zur. Kenntniss der Periarteriitis nodosa, inb. Histopathogenese, Virchows Arch. f. path. Anat. **240**:283, 1923.

2. Fishberg: Footnote 1.

3. Lamb: Periarteritis nodosa—a Clinical and Pathological Review of This Disease with Report of Two Cases, Arch. Int. Med. **14**:481, 1914.

4. Mönckeberg: Ueber Periarteriitis nodosa, Ziegler's Beitr. **38**:101, 1905. Kroetz: Zur Klinik der Periarteriitis nodosa, Deutsch. Arch. f. klin. Med. **135**:311, 1921. Walter: Beitrag zur Histopathogenese der Periarteriitis nodosa, Frankfurt. Ztschr. f. Path. **25**:306, 1921.

5. Mönckeberg: Footnote 4.

6. The extensive involvement of the veins in many organs. This also has been noted a few times only.[6]

7. The diffuse infiltration of lymph glands and spleen with eosinophils. This is mentioned by Lamb in both of his cases and therefore may have been overlooked by other investigators.

8. The finding of numerous eosinophils scattered all through the mucous membrane of the gastro-intestinal tract. This, so far as I know, is a unique observation, but this lesion may be quite common, as it is also likely to be overlooked.

9. The remarkable extension of the process from the perivascular connective tissue into myocardium and renal tissue. This has been fairly frequently seen in the case of the myocardium, but although subacute nephritis has also been observed quite often, it usually was of the nature of an apparently independent hematogenous glomerulonephritis. In our case the lesions were local extensions of the inflammatory process through the interstitial tissue, and the glomeruli were not involved or only secondarily. More limited foci of such interstitial subacute inflammation were also discovered in sections of the pancreas, prostate and muscle.

10. The comparative absence of severe lesions in the arteries of the gastro-intestinal tract.

PATHOLOGY OF PERIARTERITIS NODOSA

In spite of the obvious difficulties on account of the complexity of the disease, I shall attempt to give a brief summary of its pathology.

The clinical symptoms are always obscure, so much so that the clinical diagnosis has been made only when material from the diseased arteries was obtained by biopsy, usually from subcutaneous nodules or in one case[7] from the mesentery in the course of a laparotomy. Unfortunately, these subcutaneous nodules are present only in a small minority of the cases.

The disease attacks mostly young persons who apparently are in the best of health. The youngest victim of it was a child of 2½ years old, but it has been observed several times in persons over 50, and in one case in a man of 62. Among those afflicted the male sex predominates in a proportion of about 5:1. The average age was 31 in a long series of male cases and in a much smaller series of cases in women.

6. Beitzke: Präparate eines Falles von Periarteriitis nodosa, Berl. klin. Wchnschr. **65**:1381, 1908. Ueber einen Fall von Periarteriitis nodosa, Virchows Arch. f. path. Anat. **199**:214, 1910. Von Haun: Pathohistologische und experimentelle Untersuchungen über Periarteriitis nodosa. Virchows Arch. f. path. Anat. **227**:90, 1920.

7. Baehr: Periarteritis nodosa, Proc. New York Path. Soc. **19**:131, 1919. Manges and Baehr: Periarteritis nodosa, Am. J. M. Sc. **162**:162, 1921.

The trouble may start acutely with chills and fever or usually more insidiously. The general course is that of a chronic obscure sepsis with rapidly progressive emaciation and great weakness and prostration. The temperature curve is irregular. The fever is never high and more or less intermittent. Many observers have noticed that there are definite periods of exacerbation and remission. There is often much sweating, especially during the periods of exacerbation. The pulse rate is usually high, often quite out of proportion to the temperature. Leukocytosis is nearly always well marked and often continued and excessive. In view of the presence of so many eosinophils in the lesions, it is curious that eosinophilia has been noted a few times only—51 per cent. in one of Lamb's two cases and 30 per cent. in Lewis'[8] case, to a less extent in the case of Pickert-Menke.[9] The only other more or less constant symptom is an often severe and always very annoying intermittent pain in the abdomen. This pain has not been fully explained, because it may occur even in cases in which the abdominal arteries are only slightly involved or not at all. It may be due to peritoneal irritation. The disease in most cases progresses more or less rapidly to a fatal termination lasting from a few weeks to several months, sometimes a year or more. Recoveries have been observed in a few cases, usually after intensive antisyphilitic treatment, but they also seem to occur spontaneously, and it is suspected by some that lighter cases of the disease are not so infrequent and heal without producing any severe clinical symptoms.

Other symptoms which may arise depend very much on the localization of the disease in the arteries of various organs.

The branches of the coronary arteries are most commonly involved. In them we find the typical nodules and frequently many small aneurysms. Thromboses are also common, which may cause anemic necroses in the heart muscle. Often the disease of the coronaries is associated with a more or less extensive myocarditis. In view of these severe changes in the arteries and the musculature of the heart, it is astonishing that primary cardiac weakness is observed comparatively rarely. It was well marked, however, in our own case and in that of Hart's.[10]

The next organ in frequency of involvement is probably the kidney. Here the lesions are often severe. The nodules in the wall of the arteries are well marked, the aneurysms numerous and the frequent thrombotic obstruction of them causes the formation of many anemic

8. Lewis: Report of a Case of Periarteritis nodosa, Proc. Path. Soc. Philadelphia, n. s. **14**:134, 1911.

9. Pickert-Menke: Ueber einen Fall von Periarteriitis nodosa, Frankfurt. Ztschr. f. Path. **23**:313, 1920.

10. Hart: Footnote 1.

necrotic infarcts. The disease may also extend directly into the kidney tissue, causing a subacute interstitial nephritis, as in my case. Commonly also it is associated with an apparently hematogenous nephritis of the general type of any acute or subacute glomerulonephritis. Changes in the composition of the urine are therefore rarely missing, and in some cases death has occurred from uremia. If the aneurysms are situated rather superficially underneath the capsule, they may rupture, causing large subcapsular hemorrhages. These hemorrhages may cause death by acute anemia.[11] The lesions in the arteries may be largely limited to the kidneys, as in Fishberg's case,[2] or may extend down into renal pelvis, ureters [12] and bladder.

In few cases an involvement of the arteries of the generative organs has been described (prostate, seminal vesicles, testes, uterus). In the testes the arterial lesions may produce hemorrhagic necrosis and cause swelling and tenderness in this organ.[13]

The arteries of the spleen are often diseased and exhibit the same lesions as those in the kidneys, with the frequent production of more or less extensive and numerous infarcts in the splenic tissue. The diffuse infiltration of the pulp of the spleen and of the usually moderately enlarged lymph glands with eosinophils has already been alluded to. In the more acute cases a typical enlargement and softening of the spleen may be present like that which is observed in other acute infections.

In the liver the most characteristic change is the development of peculiar white strands of fibrous tissue which follow the course of the diseased arteries but do not usually penetrate deeply into the liver tissue proper. The arteries usually show nodular thickenings and multiple aneurysms. Extensive thromboses are frequently observed in them and may lead to the formation of infarct-like areas in the hepatic tissue. The larger arteries at the hilus of the liver may be involved, and in one case [14] death was due to rupture of an aneurysm of the hepatic artery into the peritoneal cavity.

The characteristic changes may also occur in the arteries of the gallbladder and here may lead to hemorrhages, necroses and ulceration in the wall of this organ, causing the appearance of symptoms of acute cholecystitis.

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11. Bloch, Vera: Ueber Periarteriitis nodosa, Inaug. Diss. Zürich, 1913. Walter: Beitrag zur Histopathogenese der Periarteriitis nodosa, Frankfurt. Ztschr. f. Path. **25**:306, 1921. Harris and Friedrichs: The Experimental Production of Periarteritis nodosa in the Rabbit with Consideration of the Specific Causal Excitant, J. Exper. M. **36**:219, 1922. Mertens: Ueber Periarteriitis nodosa mit Massenblutung im Nierenlager, Klin. Wchnschr. **1**:1844, 1922.

12. Oberndorfer: Ein Fall von Periarteriitis nodosa, München. med. Wchnschr. **54**:2618, 1907. Bomhard: Periarteriitis nodosa als Folge einer Staphylokokkensepsis nach Angina, Virchows Arch. f. path. Anat. **192**:305, 1908.

13. Mönckeberg: Footnote 4.

14. Klotz: Periarteritis nodosa, J. Med. Res. **37**:1, 1917.

The smaller branches of the gastric and mesenteric arteries are also frequently diseased, showing nodules and aneurysmal dilatation. The disease often extends down into the smallest branches in the submucosa of both stomach and intestines. If there is much obstruction in these smallest arteries hemorrhagic necroses and ulcerations occur in the mucous membrane. These ulcerations in the intestines may become so deep that they cause acute perforation and death from acute general peritonitis.[15] The lesions may be practically limited to the gastrointestinal tract.[16] Clinically the presence of such lesions might be suspected from the appearance of blood in the stools and from the occurrences of severe diarrhea, which was a prominent symptom in some instances.

Pains in the muscles of the extremities are common and are usually due to an extensive affection of the small branches of the arteries of the muscles with the development of many nodules and numerous small aneurysms. An especially interesting clinical picture may arise when the small arteries of the peripheral nerves are badly diseased. This may be followed by a widespread degeneration of the nerves and the symptoms of a severe progressive peripheral neuritis.[17] Here again in some cases the disease may be practically limited to the peripheral nerves and the musculature.[18] Whether these two cases are really cases of periarteritis acuta nodosa is a little doubtful. Most inter-

15. Zimmermann: Ueber zwei Fälle von nekrosirender Enteritis bei Morbus maculosus Werlhofii, Wagners Arch. f. Heilk. **15**:167, 1874. Lorenz: Beitrag zur Kenntnis der multiplen degenerativen Neuritis, Ztschr. f. klin. Med **18**:493, 1891. Versé: Ueber Periarteriitis nodosa, München. med. Wchnschr. **38**:1809, 1905. Periarteritis nodosa und arteritis syphilitica cerebralis, Ziegler's Beitr. **40**:409, 1907. Beitzke: Präparate eines Falles von Periarteriitis nodosa, Berl. klin. Wchnschr. **65**:1381, 1908. Ueber einen Fall von Periarteriitis nodosa, Virchows Arch. f. path. Anat. **199**:214, 1910. Meyer, S.: Zur klinischen Erkenntnis der Periarteriitis nodosa und ihre pathologisch-anatomischen Grundlagen, Berl. klin. Wchnschr. **58**:473, 1921.

16. Veszprémi: Ueber die Periarteriitis nodosa, Zieglers Beitr. **52**:476, 1912.

17. Kussmaul and Maier: Ueber eine bisher nicht beschriebene eigentümliche Arterienerkrankung (Periarteriitis nodosa), Deutsch. Arch. f. klin. Med. **1**:484, 1866. Meyer, P.: Ueber Periarteriitis nodosa oder multiple Aneurysmen der mittleren und kleineren Arterien, Virchows Arch. f. path. Anat. **74**:277, 1878. Rosenblath: Ein seltener Fall von Erkrankung der kleinen Arterien der Muskeln und Nerven, die klinisch als Dermatomyositis imponierte, Ztschr. f. klin. Med. **33**:547, 1897. Freund: Zur Kenntnis der Periarteriitis nodosa, Deutsch. Arch. f. klin. Med. **62**:537, 1899. Lorenz: Beitrag zur Kenntnis der multiplen degenerativen Neuritis, Ztschr. f. klin. Med. **18**:493, 1891. Schmincke: Ueber Neuritis bei Periarteriitis nodosa, Verh. d. Deutsch. path. Ges. **18**:287, 1921. Meyer, S.: Zur klinischen Erkenntnis der Periarteriitis nodosa und ihre pathologisch-anatomischen Grundlagen, Berl. klin. Wchnschr. **58**:473, 1921. Gerlach: Ueber Periarteriitis nodosa. Klin. Wchnschr. **1**:467, 1922.

18. Damsch and Seitzke: Ueber einen Fall von akuter Erkrankung der gesammten Körpermuskulatur der Kleinen Muskel und Nervenarterien, Festschrift für Orth, 1903. Joffroy and Achard: Nervite periphérique d'origine vasculaire, Arch. de méd. Exper. **1**:229, 1889.

esting in this connection is the case of Fränkel-Wohlwill.[19] In this patient, the arteries in the kidneys and in the stomach were badly diseased. There was also a marked peripheral neuritis, but Wohlwill reports that the arteries in the affected nerves were not diseased. He concludes that the lesions in the nerves were evidently due to some general toxic condition associated with the disease.

While the peripheral nerves are so frequently diseased, the central nervous system usually escapes entirely. Only four cases are on record in which the cerebral arteries were involved. In two of these [20,21] multiple aneurysms had developed, one of which had ruptured, in another [22] the disease was limited to the small vessels of the pia, and multiple small hemorrhages were found in the brain substance,[23] and in the last one [24] there was present a large area of softening due to thrombosis of a diseased artery.

The nodules which sometimes occur in the small arteries of the skin have already been mentioned, also the important rôle which they play in the clinical diagnosis of the disease.[25] The little aneurysm which may form in them may rupture and give rise to the production of hematomata.[26] In connection with the skin, attention should be called to the fact that in quite a number of cases various eruptions have been described, such as multiple erythematous spots, with and without hemorrhages, purpura rheumatica, crops of urticaria, and in one instance a typical erythema nodosum.[14]

Aneurysms also sometimes form along the course of the superficial palpable arteries. They have been observed in connection with the temporal and brachial arteries.

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19. Fränkel: Periarteriitis nodosa, München. med. Wchnschr. **64**:1538, 1917, and Wohlwill: Periarteriitis nodosa, Berl. klin. Wchnschr. **55**:94, 1918.

20. Chvostek and Weichselbaum: Herdweise syphilitische Endarteriitis mit multipler Aneurysmenbildung, Allg. Wien. med. Ztschr. **22**:257, 265, 275, 294, 312, 1877.

21. Dickson: Polyarteritis acuta nodosa and periarteriitis nodosa, J. Path. & Bacteriol. **12**:31, 1908.

22. Müller: Ueber Periarteriitis nodosa, Fetschr. d. städt. Krankenh. Dresden-Friedrichstadt, Dresden, 1899, p. 458.

23. This case is also interesting because Müller in it discovered typical lesions in the retinal arteries. A more careful investigation of the eyes in future cases would seem to be indicated.

24. Longcope: Periarteritis nodosa, with Report of a Case with Autopsy, Bull. Ayer Clin. Lab. Penn. Hosp. **5**:1, 1908.

25. Kussmaul and Maier: Ueber eine bisher nicht beschriebene eigentümliche Arterienerkrankung (Periarteriitis nodosa), Deutsch. Arch. f. klin. Med. **1**:484, 1866. Müller: Festschr. d. städt. Krankenh. Dresden-Friedrichstadt, 1899, p. 458. Freund: Deutsch. Arch. f. klin. Med. **62**:537, 1899. Schmorl: Diskussion über Bendas Vortrag über "Aneurysma und Syphilis," Verh. d. Deutsch. path. Ges. **6**:203, 1903. Von Haun: Virchows Arch. f. path. Anat. **227**:90, 1920.

26. Benedict: Ueber Periarteriitis nodosa, Ztschr. f. klin. Med. **64**:405, 1907.

As stated above, lesions in the bronchial arteries have been noted occasionally, but a diffuse infiltration of the bronchial mucous membrane with asthmatic symptoms seems to be one of the unique feautres in our case.

It is also difficult to understand why in most cases the pulmonary vessels should be entirely exempt and in Mönckeberg's [5] and my cases so badly diseased with marked extension of the subacute inflammation into the adjoining pulmonary tissue.

The liability of the serous membranes to participate in the process has not been sufficiently recognized. This was quite a marked feature in our case and the presence of a true exudate in the pleural cavities was quite a puzzle to the clinicians. The occurrence of subacute pericarditis, pleurisy or peritonitis or several of these conditions in various combinations has been described in many cases, but no special attention has been paid to it and too little emphasis has been placed on the appearance of rather characteristic, just visible, grayish nodules in these lesions.

In conclusion, it may be stated that minor lesions have been observed in the arteries of several other organs, sometimes with more or less involvement of the parenchyma, as, for instance, of those in the pancreas or the suprarenals.

It may be readily imagined what a bewildering variety of symptoms may arise when not one, but several systems are simultaneously involved, as is usually the case. It is to be feared, therefore, that in spite of our better knowledge of the disease successful clinical diagnosis will remain a rare exception. The fact that clinicians see it so rarely will naturally contribute to this result; there are several, however, who have observed more than one case (Kussmaul,[27] Müller,[22] Lamb,[4] Klotz,[14] Vesprémi [28]). Several cases have been seen at Fischer's laboratory in Frankfurt; five or more under Marchand at the Pathological Institute at Leipzig (Ferrari,[29] Versé [30]); three in Philadelphia (Longcope,[24] Cooke,[31] and Lewis [8]). This would seem to indicate that the disease is not so excessively rare as was believed at one time.

27. Kussmaul and Maier: Deutschr. Arch. f. klin. Med. **1**:484, 1866.

28. Veszprémi and Janscó: Zieglers Beitr. **34**:1, 1903. Veszprémi, Ibid. **52**:476, 1912.

29. Farrari: Ueber Periarteriitis nodosa und ihre Beziehungen zur Polymyositis und Polyneuritis acuta, Zieglers Beitr. **34**:350, 1903.

30. Versé: Ueber Periarteriitis nodosa, München. med. Wchnschr. **38**:1809, 1905. Periarteriitis nodosa und arteriitis syphilitica cerebralis, Zieglers Beitr. **40**:409, 1907. Diskussion zum Vortrag Jägers über vergleichend path. Untersuchungen über Periarteriitis nodosa, Verh. d. deutsch. path. Ges. **13**:213, 1909. Ueber totale Pfortader-obliteration und anämische Infarkte der Leber, ibid., p. 314. Periarteriitis nodosa, München. med. Wchnschr. **64**:1468, 1917.

31. Cooke: A Case of Periarteritis nodosa, Proc. Path. Soc. Philadelphia, n. s. **14**:96, 1911.

The histologic lesions are of a distinctly inflammatory character, although the destructive lesions in the media may prevail to such an extent that the signs of inflammation may be overlooked, especially with the more imperfect histologic methods in use at the time when some of the first cases were examined by Rokitansky [32] and Eppinger.[33] Rokitansky suggested that the multiple aneurysms might be due to multiple tears in the musculo-elastic coat, and Eppinger attempted to explain this by assuming the presence of a congenital weakness of the wall of the diseased arteries. Practically all later authors agree on the inflammatory nature of the disturbance. One of the most characteristic features of it in the early cases is a tremendous infiltration of the adventitia with partly neutrophilic, partly eosinophilic polymorphonuclear leukocytes mixed with a smaller or larger proportion of small lymphocytes and plasma cells. Degenerative lesions in the media tending to the destruction of muscle and elastic tissue in some cases are early and severe, so that the arteries may actually rupture, and hematomas or false aneurysms may develop. Usually the degenerative changes in the media are more moderate and of slower development, beginning with a peculiar vacuolization of the musculature and ending in a more or less rapidly progressive destruction of the elastic fibers. The diseased muscle is invaded early by the leukocytes, and these may soon find their way into the intima. The behavior of this coat varies considerably. In some cases it remains practically unaltered; in others, it shows a marked collection of fluid underneath the endothelium, which, when hardened, coagulates into a hyaline substance in which there may be masses of fibrin. Soon proliferative changes also become noticeable. These begin in the inner layer of the adventitia close to the muscle. Large masses of cells resembling epithelioid cells are found in this region. These promptly begin to invade the diseased musculature. Among these cells one also finds new capillary blood vessels, and it is these cells that show the tendency to arrange themselves in small cellular nodules which are often situated partly in the adventitia, partly in the destroyed muscle. The nodules are rich in small capillaries. They do not show any tendency to central degeneration or to caseation. Giant cells have not been found in them, although foreign body giant cells have been seen in one case in the media, which was the seat of a rapid disintegration. This new cellular tissue may run on into the intima or there may be a separate proliferation of the intimal cells as in our case, with later production of fibrous tissue in both places. Whether aneurysms form

32. Rokitansky: Ueber einige der wichtigsten Krankheiten der Arterien, Denkschr. d. K. Akad. d. Wissensch Wien **4**:1, 1852.

33. Eppinger. Pathogenese, Histogenese und Aetiologie der Aneurysmen. Das congenitale Aneurysma, Arch. f. klin. Chir. **35**: Suppl. 42, 1887.

depends first, on the extent of destruction in the musculature, and secondly, on the amount and resistance of the new fibrous tissue. If the latter is voluminous, the lumen of the vessels is likely to be more or less completely obstructed. Since the disease is usually focal, these masses of fibrous tissue in the wall of the small arteries produce a more coarsely nodular appearance. The still larger nodules, from the size of the kernel of a cherry or larger, are usually aneurysms, which may become solidified by the organization of thrombus in them. These multiple small aneurysms are the most striking phenomenon in many of the older cases. They are not essential and are purely secondary developments.

A discussion of the exact seat of the primary lesions in the wall of the affected arteries, I believe, is futile, because soon all three coats become involved in the process.

ETIOLOGY OF PERIARTERITIS NODOSA

The question of the etiology of the condition is of much greater importance. In regard to this, three theories have been advanced and are being supported by more or less convincing arguments by the various writers.

At the suggestion of Virchow, who had seen some of the sections of Kussmaul's case, Kussmaul tentatively mentioned the possibility of a syphilitic origin, and since then this idea has found several advocates, most prominent among them being Versé, who has seen more cases of this disease than any one else. In one of his papers published in Ziegler's *Beiträge* in 1907, he makes a careful comparison between the findings in his case [34] and several specimens of true syphilitic arteritis, and he arrives at the conclusion that the lesions in the two diseases are quite similar. He is therefore inclined to believe that the disease may be a modified form of syphilis. The existence of a certain similarity, especially in the older lesions of the two diseases, is undeniable, but the incipient stages are quite different; the heavy infiltration with granular leukocytes does not occur in syphilis; the granulomas which form later do not caseate; the accumulation of a serofibrinous exudate also points to a much more active inflammatory process than that which is caused by *Spirochaeta pallida*. The comparative rarity of a syphilitic history in patients suffering from periarteritis and the almost constant absence of a Wassermann reaction also speak against a connection of the lesions with a syphilitic infection. If the lesions were truly syphilitic, they would be of an exceptionally acute nature and therefore should contain the infectious agent in large numbers. In sixteen cases of periarteritis nodosa spirochetes have been searched

34. Versé: Zieglers Beitr. **40**:409, 1907.

for in sections, but with a uniformly negative result. The fact also that a disease identical with periarteritis nodosa occurs in various animals seems to make it impossible to accept syphilis as an etiologic factor. Some believe that it may act as a predisposing factor, but even this appears doubtful.

If we exclude syphilis, as I think we are justified in doing, there remain two other possibilities which have been widely discussed: (1) The disease is a special infection, "sui generis," or (2) the lesions are the result of the action on perhaps predisposed arteries of various infectious or toxic agents, the latter having been suggested on account of the general inability to demonstrate bacteria in the sections.

The idea of a special infection derives its main support from these facts: (1) A disease practically identical with it has been observed by Lüpke [35] in epidemic form in a herd of stags; (2) twice (v. Haun [36] and Harris and Friedrichs [37]) the claim has been made that there has been a successful experimental transmission of the disease to laboratory animals. The experiments reported by von Haun are hardly convincing. He inoculated guinea-pigs intraperitoneally with blood obtained from a patient suffering from periarteritis nodosa and again inoculated other guinea-pigs from these when they were sacrificed two months later. No gross lesions were seen in any of the inoculated animals. Microscopic examination revealed suspicious lesions about some of the smaller organ arteries, but von Haun states that these vascular lesions were not pronounced, and he doubts whether the guinea-pig is a suitable animal for such experiments. Lamb [3] had inoculated guinea-pigs before von Haun, but with negative results, and Carling and Hicks [38] recently repeated von Haun's experiments in exactly the same way. They even permitted some guinea-pigs to live longer than two months, but could not detect any characteristic lesions in them either grossly or microscopically.

The experiments of Harris and Friedrichs were performed on rabbits, in a more elaborate manner. They injected emulsions from

35. Lüpke: Ueber Periarteriitis nodosa bei Axishirschen, Verh. der deutsch. path. Ges. **10**:149, 1906. A histologic study of the lesions is given by Jaeger: Die Periarteriitis nodosa, Virchows Arch. f. path. Anat. **197**:71, 1909. The disease has also been found in other animals; in cattle, by Guldner: Virchows Arch. f. path. Anat. **219**:366, 1915; and in hogs by Joest: Ziegler's Beitr. **69**:85, 1921.

36. Von Haun: Pathohistologische und experimentelle Untersuchungen über Periarteriitis nodosa, Virchows Arch. f. path. Anat. **227**:90, 1920.

37. Harris and Friedrichs: The Experimental Production of Periarteritis nodosa in the Rabbit, with a Consideration of the Specific Causal Excitant, J. Exper. M. **36**:219, 1922.

38. Carling and Hicks: A Case of Periarteritis nodosa Accidentally Recognized During Life, The Lancet **1**:1001, 1923.

the diseased tissues intravenously into two rabbits, and from these they inoculated others with filtered and unfiltered tissue emulsions. The animals lived from two to six and one-half months. None of them showed gross lesions except rabbit C, which died after one month. This animal showed some rather coarse nodules in the lungs, which may have been due to embolism. The authors give photomicrographs of the lesions, among which Figures 8 and 11 are suggestive of a positive result. I believe, however, that even these experiments are not entirely convincing. Lamb also reports negative inoculation experiments in rabbits, and our own experiments with the same animal have been negative. It must be stated, however, that the first inoculations by us were made about thirty-six hours after necropsy and not intravenously but intraperitoneally.

Whatever the final result of this experimental work may be, it is of value to look at the question from one more point of view and to study the apparently close relation which exists between periarteritis nodosa and the ill-defined group of subacute and chronic "septic" conditions with so-called "rheumatic" symptoms and frequently associated with endocarditis. Of the close pathologic relationship of these "rheumatic" processes there is no doubt, but whether they form an etiologic entity also by being caused by various types of streptococci is not quite so certain. There are some, however, who still believe that rheumatic fever is caused by some as yet unknown special infectious agent. One need not study many cases of periarteritis to discover its close relation to this group. This has been commented on by many authors. The evidence connecting the two conditions is of all kinds—clinical, pathologic and bacteriologic. In several cases,[39] there is a definite history of a recent attack of rheumatism; in others, the disease was ushered in by an acute attack of tonsillitis,[40] in one case with abscess formation.[41] During the course of the illness almost all clinicians have been impressed with the resemblance of the syndrome to that of a slow, comparatively mild septic condition, and various skin eruptions have been observed which seemed to favor this impression. These were either erythematous or resembled purpura rheumatica.[42] In one case,[28] the efflorescences were more of an urticarial nature and

39. Rosenblath: Ztschr. f. klin. Med. **33**:547, 1897. Müller: Festschr. d. städt. Krankenh. Dresden-Friedrichstadt, Dresden, 1899, p. 458.

40. Oberndorfer: München. med. Wchnschr. **54**:2618, 1907 and Bomhard: Virchows Arch. f. path. Anat. **192**:305, 1908. Hart: Berl. klin. Wchnschr. **45**:1305, 1908; and Künne: Frankfurt. Ztschr. f. Path. **5**:105, 1910. Lamb: Arch. Int. Med. **14**:481, 1914. Klotz: J. Med. Res. **37**:1, 1917. Mertens: Klin. Wchnschr. **1**:1844, 1922.

41. Walter: Beitrag zur Histopathogenese der Periarteriitis nodosa, Frankfurt. Ztschr. f. Path. **25**:306, 1921.

42. Zimmermann: Wagners Arch. f. Heilk. **15**:167, 1874. Schreiber: Inaug. Diss. Königsberg, 1904. Lamb: Arch. Int. Med. **14**:481, 1914.

Klotz'[14] case showed a typical erythemia nodosum. In one of the most acute cases of the whole series,[2] the disease developed immediately following an injury to the hand, with consecutive abscess formation in the soft parts of the upper arm. Unfortunately there is no record of a bacteriologic examination of the abscess, but the opening of it was followed by an erysipelatous condition of the adjoining skin. During the course of the disease an erythema appeared on the skin elsewhere, which wandered from one place to another and in the end also showed a great resemblance to erysipelas. The patient in Schrieber's case[43] was suffering from chronic nonsyphilitic ulcers of the skin of the legs when the disease developed, and the patient in Lewis'[8] had an infected lacerated wound of the scalp. Kroetz' patient[44] had a septic infection of the urinary tract. Endocarditis was present in five cases.[45] It was mostly acute, in some cases more chronic. In Lamb's, diplostreptococci were found on the diseased heart valves and in other parts of the body.

In the discussion of Lüpke's paper before the German Pathologic Society, Aschoff pointed out that apart from the possibility of a syphilitic origin in periarteritis nodosa, a rheumatic infection also should be considered in view of the similarity of the "rheumatic" nodules to the small granulomatous nodules in periarteritis. The rheumatic nodules, although usually confined to the adventitia, might destroy the media deeply. (A characteristic case of this kind is given by Geipel: Myocarditis, München. med. Wchnschr. 54: 1057, 1907.)

If it is true that certain forms of nephritis are caused by infections of this character, the frequent coincidence of periarteritis nodosa and acute and subacute glomerulonephritis is highly suggestive.[46] In this connection, it is interesting to recall that in early glomerulonephritis eosinophils are commonly found in the lesions.

So far as the actual finding of streptococci is concerned, their presence has never been demonstrated in the lesions in spite of the

43. Schreiber: Ueber Periarteriitis nodosa, Inaug. Diss. Königsberg, 1904.

44. Kroetz: Deutsch. Arch. f. klin. Med. **135**:311, 1921.

45. Müller: Festschr. d. städt. Krankenh. Dresden-Friedrichstadt, Dresden, 1899, p. 458. Benda: Ueber die sog. Periarteriitis nodosa, Berl. klin. Wchnschr. **45**:353, 1908. Lewis: Report of a Case of Periarteritis nodosa, Proc. Path. Soc. Philadelphia, n. s. **14**:134, 1911. Lamb: Arch. Int. Med. **14**:481, 1914. Löwenberg: Beitrag zur Klinik der Periarteriitis nodosa, Med. Klin. **19**:207, 1923.

46. Graf: Ueber einen Fall von Periarteriitis nodosa mit multipler Aneurysmenbildung, Zieglers Beitr. **19**:181, 1896. Rosenblath: Ztschr. f. klin. Med. **33**:547, 1897. Freund: Deutsch. Arch. f. klin. Med. **62**:537, 1899. Dickson: Polyarteritis acuta nodosa and periarteriitis nodosa, J. Path. & Bacteriol. **12**:31, 1908. Oberndorfer: München. med. Wchnschr. **54**:2618, 1907. Bomhard: Virchows Arch. f. path. Anat. **192**:305, 1908. Longcope: Bull. Ayer Clin. Lab. Penn. Hosp. **5**:1, 1908. Veszprémi: Zieglers Beitr. **52**:476, 1912. Lamb: Arch. Int. Med. **14**:481, 1914. Klotz: J. Med. Res. **37**:1, 1917.

fact that sections have been carefully examined bacteriologically in about one half of the cases. Bomhard [12] reports finding few cocci in the peripheral zone of the lumen of a blood vessel, and Longcope [24] observed a few cocci in sections of the kidney. Blood cultures during life which were made in ten cases, sometimes repeatedly, uniformly remained sterile with the one exception of one flask in our case which contained streptococci. Beitzke [47] isolated streptococci from the heart blood at necropsy. In our case, a guinea-pig which was inoculated intraperitoneally with an emulsion of diseased tissue died of acute streptococcic peritonitis. I have already mentioned that in Lamb's [3] case a typical diplostreptococcus endocarditis was present. Beattie and Douglas [48] obtained a pure culture of streptococci from the subcapsular hemorrhage in the right kidney. Jonas [49] found streptococci in a culture from the kidney. Lamb's [3] careful cultural work was entirely negative, except for his recovering streptococci in a tissue culture from one of the aneurysms of the heart. The whole question of the relation of streptococcus infection to the disease has been most carefully studied by Klotz. In both of his cases [14] he recovered streptococci, in the first one from the gallbladder (*Streptococcus mitis*) and in the second one from the heart blood, bile, subcapsular lymph channels of the liver (*Streptococcus anginosus* or *Streptococcus salivarius*). He also attempted to reproduce the characteristic lesions of the disease by inoculating the streptococci obtained from his cases about the celiac axis and into the anterior mediastinum of rabbits. *Streptococcus anginosus* proved too virulent, killing the animals in twenty-four hours, but with the less virulent cultures at times a subacute periarteritis with slight involvement of the media was obtained. On the whole, there is not much direct evidence of the importance of the streptococcus in periarteritis nodosa, but this is true also of other manifestations of this group of rheumatic conditions, the connecting link between which is not plainly apparent at the present time. It is possible that in such rheumatic conditions the streptococcus may play only the rôle of a frequent secondary invader.

Do these observations on periarteritis acuta nodosa add anything to our understanding of the more chronic diseases of the arteries in particular to our knowledge of arteriosclerosis? In the chronic cases of periarteritis marked scarring of the walls of the affected arteries eventually develops, and a condition arises not dissimilar to severe arteriosclerosis of the peripheral arteries, although the lesions are

47. Beitzke: Berl. klin. Wchnschr. **65**:1381, 1908. Virchows Arch. f. path. Anat. **199**:214, 1910.

48. Beattie and Douglas: A Case of Periarteritis Nodosa, J. Path. & Bacteriol. **17**:194, 1912-1913.

49. Jonas: Periarteritis Nodosa, München. med. Wchnschr. **59**:1685, 1912.

usually more focal in character and associated with more cicatrization in media and adventitia than that which we ordinarily find in simple arteriosclerosis. Any one who has studied an extensive pathologic material must recall cases of especially severe arteriosclerosis of the peripheral arteries with much scarring, with a marked tendency to dilatation and even to the development of aneurysms. There are transitions from such cases to the more common type of arteriosclerosis in which the lesions are more strictly confined to the intima. Personally, I should feel inclined to group all these changes together as arterial inflammations, particularly as I am becoming convinced more and more that primarily arteriosclerosis is due to a true inflammation of the arterial wall, only modified later on by degenerative and reparative processes. This would, of course, not mean that we should postulate an acute inflammatory beginning like that observed in cases of periarteritis for all cases of chronic arteriosclerosis. The severe forms which I have alluded to actually may have a more acute beginning than we are now inclined to believe. In fact, our general experience in this regard makes it quite probable that we have been unduly skeptical in trying to visualize the early stages of this and other chronic inflammatory conditions. When we do see these early lesions we are usually amazed at the tremendous involvement of the tissues. I believe, however, that it is equally clear that even the earliest lesions in ordinary arteriosclerosis are mild in character when compared with those in periarteritis; but this should not prevent us from trying to apply the lessons taught by the more acute disease to the more chronic conditions. In this way we might obtain some clues in regard to the etiologic possibilities of the more obscure chronic conditions; we might also understand better their histogenesis and that of the lesions in the various organs which are so commonly associated with them.

CONCLUSIONS

1. Periarteritis nodosa is an acute inflammatory disease of the smaller arteries, usually focal in character, which may involve any and all vascular territories.

2. It probably starts in the adventitia, but soon involves all coats of the arterial wall and leads to the development of microscopic granulomatous nodules, later to coarser fibrous nodules in the wall of the affected arteries, and eventually to the formation of multiple aneurysms. Thrombosis is common in the diseased arteries and may lead to necroses in the tissues (infarcts, hemorrhagic necroses and ulcers).

3. The inflammation may extend from the arteries into the adjoining tissues. The serous and mucous membranes are likely to become involved in the process.

4. The etiology of the disease remains obscure, but the observations suggest some relation to subacute "septic rheumatic" infections.

5. The clinical picture of the disease is that of a subacute infection with local symptoms resulting from the more or less marked involvement of various organs.

ABSTRACT OF DISCUSSION

Dr. H. E. Robertson, Rochester, Minn.: I believe that periarteritis nodosa is much more common than is ordinarily supposed. It is probably true that virtually every granulomatus infection in the body gives rise to periarteritis nodosa to a certain extent. We do not term it that because the involvement of the arteries is often not the chief feature of the disease. In this particular disease it would seem that we were dealing not so much with a special cause as with a tissue specificity. Perhaps that is a distinct disease, but the chances are probable that we are dealing with a form of rheumatic disease in which we have a tissue specificity; and this is true practically of every type of rheumatism with which we have to deal. If we could only determine its specificity—its pathogenicity we call it, but it is really its specificity—we could probably get a stage in a particular subject or particular animal at which any organism might produce this sort of picture.

Dr. William Ophüls, San Francisco: Aschoff himself has suggested the great similarity, at times, of these granulatomas in periarteritis and his rheumatic nodules. A case in point has been published by Geipel. So far as the frequency of the disease is concerned, I may say this: that as the disease has become better known it has apparently become more frequent. There are also some investigators who have seen several cases. For instance, Versé in Germany has mentioned in literature four or five cases and probably has seen more; in our own country there were three observed in Philadelphia within a comparatively short time. So the disease is one that, when carefully searched for microscopically, is comparatively frequently found. It may very well be overlooked if microscopic sections are not made. Predisposition certainly plays a marked rôle in it. It is only special types of individuals who develop periarteritis nodosa.

THE BACTERIOPHAGE IN THE TREATMENT OF INFECTIONS *

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It is premature to draw elaborate conclusions regarding the efficacy of the bacteriophage in the treatment of infections. However, we feel that our success in a number of cases is of sufficient importance to present these cases at this time.

The bacteriophage was found by d'Herelle [1] in 1917 in the stools of patients convalescing from dysentery. The filtrates from broth cultures of these stools exhibited an interesting phenomenon. When added in amounts varying from 2 drops to 2 c.c. to young broth cultures of Shiga dysentery, it was found that these bacterial suspensions became limpid after a few hours in the incubator and were as clear as water. When agar slant subcultures were made from these tubes, after several hours' incubation one noted either a sterile slant (a pure culture of the bacteriophage) or multiple minute round clear areas in which no bacteria grew, and these d'Herelle has called "colonies" of bacteriophages. Touching one of these clear areas with a sterile platinum loop, this "lytic substance" could be transplanted to other young broth suspensions of Shiga dysentery bacilli, and the phenomenon would again be repeated.

Here, then, is a "substance" isolated from the intestinal tract of man which possesses the property of actually dissolving bacteria and which grows or increases at the expense of bacteria. It cannot be described accurately as bactericidal or germicidal, but it is lytic in that the organisms are completely destroyed without fragments remaining. In 1915, Twort [2] observed a similar phenomenon, perhaps the same, though there is still controversy regarding this. It is possible, however, that Hankin [3] in 1896 first observed the phenomenon in the waters of certain rivers in India when working with the cholera vibrio, though we cannot be sure of this.

In brief, the bacteriophage is a "lytic substance" which has the property of dissolving bacteria. D'Herelle believes it to be a living organism which parasitizes bacteria, although others have thought it to be enzymatic in nature.

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* From the Department of Bacteriology and Preventive Medicine, Baylor University College of Medicine.

1. D'Herelle, F.: The Bacteriophage, English edition, March, 1922.

2. Twort, F. W.: An Investigation on the Nature of Ultra-Microscopic Viruses, Lancet, **2**:1241, 1915. Researches on Dysentery, Brit. J. Exper. Path. **1**:237, 1920.

3. Hankin, E. H.: L'Action bactéricide des eux de la jumna et du gange, Lancet **10**:511-523, 1896.

In Part 2 of d'Herelle's book he discusses the bacteriophage in disease. He reports five cases of bacillary dysentery in patients from 6 to 70 years of age. All five cases were due to the Shiga bacillus. In the stools in each case the bacteriophage was present and active against the infecting organism. All of these patients recovered. Recovery, according to d'Herelle, was due to the presence of the bacteriophage in the intestinal tract. A sixth patient, a man, aged 56, was infected with the Hiss strain. A bacteriophage was isolated which was lytic for a stock strain of the Hiss bacillus, but only after twelve subcultures of the Hiss strain from the patient (in other words, when the organism was attenuated) did the bacteriophage become completely lytic for that organism. This case terminated fatally, and at necropsy the Hiss bacillus was isolated from the heart blood. D'Herelle believes this was a case of B. dysenteriae Hiss septicemia, and that death ensued because of failure of the intestinal bacteriophage to adapt itself to the Hiss strain responsible for the patient's infection. In other words, in disease there appears to be a conflict between the infecting organism and the bacteriophage, and the disease has a fatal issue when the bacteriophage exerts no protective action through lack of adaptation to the infecting organism, or when the pathogenic organism acquires a resistance to the bacteriophage, a "refractory state" so called. In a series of other infections, including pyelonephritis (*B. coli*), typhoid fever (mild and severe cases), avian typhosus (in epizootics and also where epizootics did not exist), in barbone (hemorrhagic septicemia of the buffalo) and in rats harboring *B. pestis*, d'Herelle succeeded in isolating the bacteriophage which was lytic for the infecting organism in question. All of this work is interesting from the comparative standpoint, but I shall not attempt to abstract it here since it is described in detail in the literature.

D'Herelle reported five cases of bacillary dysentery in patients from 3½ to 12 years of age, all of which were due to Shiga dysentery. In each case the only treatment instituted was the ingestion of the culture of the bacteriophage. All of these patients were having bloody stools, one as few as five to seven a day, and others so many that they could not be counted. All of these patients were cured bacteriologically and clinically and were discharged from the hospital from nine to fourteen days after admission.

Bruynoghe and Maisin [4] have reported the successful use of the bacteriophage by subcutaneous injections in conditions due to the staphylococcus and anthrax. Beckerich and Hauduroy [5] have reported five

4. Bruynoghe, R., and Maisin, J.: Essais de thérapeutique au moyen du bactériophage du staphylocoque, Compt. rend. Soc. de biol. **85**:1120-1121, 1921.

5. Beckerich, A., and Hauduroy, P.: Le bactériophage dans le traitement de la fièvre typhoide, Compt. rend. Soc. de biol. **86**:168, 1922.

cases of true typhoid fever and two cases of paratyphoid B infection treated with the bacteriophage. Three of these patients received the treatment by simultaneous injection and ingestion, and the others by ingestion alone. They state that within forty-eight hours defervescence with euphoria occurred, and the apyrexia remained permanent. Two cases of typhoid fever in adults of the ataxo-adynamic form were also reported by these authors. Both of these patients were said to have pronounced myocardial involvement. The apyrexia followed the treatment within forty-eight hours, but both cases terminated fatally. The authors suggested that in these cases failure was probably due to a too long delayed intervention or to too small a dose in view of the severity of the infection. The usual amount given by mouth was 2 c.c. and 1 c.c. by injection subcutaneously. These authors describe a sudoral crisis which followed the administration in about two hours. Two cases of puerperal pyelocystitis were also reported by them due to *B. coli*. Each patient received 1 c.c. of an anticoli bacteriophage culture subcutaneously, and a permanent apyrexia ensued within forty-eight hours.

Courcoux [6] has reported a case of pyelonephritis, the first symptom of which was observed in a young woman at the sixth month of pregnancy. The bacteriophage was given by subcutaneous injection and by the injection of 15 c.c. directly into the bladder. He states that there was considerable reaction for forty-eight hours, and then all symptoms subsided, the improvement amounting to a clinical cure, although *B. coli* could still be cultivated from the urine.

Davison [7] has reported a series of twelve cases of bacillary dysentery in children, who were treated with the bacteriophage. He concludes that the treatment did not influence the mortality or course of the disease. He suggests that failure in these cases might be due to the fact that in the majority the treatment was commenced late in the disease. The only two patients treated within the first week of the onset of the disease recovered.

Our cases represent a variety of infections. We have administered the bacteriophage by nearly every route possible except intravenously and intraspinally. We have administered the material in amounts varying from 1 c.c. up to 50 c.c. At the outset we decided that some method should be devised of standardizing the bacteriophage so that we would have some fairly definite idea of the amount we were giving. We have obtained our bacteriophages from a variety of sources

6. Courcoux, A.: Pregnancy Pyelonephritis, Bull. et mém. Soc. méd. d. hôp. de Paris **46**:1151, 1922.

7. Davison, W. C.: The Bacteriolysant Therapy of Bacillary Dysentery in Children, Am. J. Dis. Child. **23**:531-534, 1922.

(McKinley[8]). A sample sent us by d'Herelle has been used for a control in testing our various filtrates. The standard we have adopted in measuring the strength of our material is simple. When we have tested a filtrate and found it to be positive for bacteriophages, the virulence has been increased by the technic described by d'Herelle until sterile agar slant subcultures are obtained. At this point the filtrate (usually from 30 to 50 c.c.) is placed in a large sterile test tube, and 1 c.c. of a twelve-hour broth culture of the organism (from stock) containing two billion organisms is added to the filtrate. The filtrate is incubated for twenty-four hours. If the filtrate is lytic for this number of bacteria, the process is repeated on the second day, at which time 2 c.c. of a twelve-hour broth culture of the organisms are added. The filtrate is again incubated for twenty-four hours. It usually remains clear, and the process is repeated on the third day with 3 c.c. of a fresh young broth culture of the organism for which we are building the bacteriophage. On the fourth day, 4 c.c. of broth culture are added, and on the fifth day, 5 c.c. The result is a filtrate lytic for a total of about thirty billion bacteria in six days, for ten billion of which it had been lytic on the last day. If the filtrate remains clear, it is of course unnecessary to filter, but as a precaution we have always filtered the material and incubated the filtrate for twenty-four hours to prove its sterility before administering it to the patient. In the following cases we have used filtrates containing bacteriophages of the standardized strength I have described and adapted to the organism (McKinley[9]) causing the patient's infection.

REPORT OF CASES

Case 1.—C. F. V., a dental student, a man, aged 41, married, came to see me on Dec. 20, 1922. The family history was not important. He had had gonorrhea in 1900 and malaria in 1911, from which he was not entirely free until 1914. He had never used alcohol. He had used tobacco since he was 17. The present illness began in June, 1918, while he was in France, with diarrhea, frequency of urination and exhaustion. He passed from ten to twelve stools a day without blood, with little odor but considerable mucous. After two weeks' rest in the hospital, he was somewhat relieved. Four weeks later he noticed a dull aching pain and a tender area about the size of a quarter beneath the costal margin on the right side, especially marked following heavy work, long hikes, etc. On September 24, he fell exhausted and was taken to the hospital, where a diagnosis was made of mucous colitis, gastritis and probably appendicitis. He rested in the hospital for about a month, and then returned to the troops. He said that the frequency of urination had continued, and he now began to notice pain and smarting in the urethra. His condition remained about the same until March, 1919, when he passed about a quarter of a tea cup of creamy white, frothy material that burned and smarted exceedingly. His condition has remained the same until the present time. He now complains of a dull

8. McKinley, E. B.: Further Notes on d'Herelle's Phenomenon, 1923 J. Lab. & Clin. Med., in press.

9. McKinley, E. B.: Notes on d'Herelle's Phenomenon, J. Lab. & Clin. Med. **8**:311-317, 1923.

aching pain at times radiating from the scrotum on the left side up to the abdomen. His best weight was 165 pounds (74.84 kg.), twenty years ago. His present weight is 133 pounds (60.3 kg.) and he says that he has been gradually losing weight since 1918. The Wassermann test was negative.

Laboratory Examinations.—The gastric content showed a deficiency in hydrochloric acid. The bile and blood were normal. The urine showed no albumin, no sugar and no casts, but occult blood was present on three examinations.

Treatment and Course.—Dr. H. L. Cecil was asked to see the patient, and a diagnosis of stone in the left kidney was made, which was confirmed by roentgen-ray examination. Dr. Cecil removed this stone on January 1. The patient made a rapid and uneventful recovery.

January 17: Examination of catheterized specimens from each kidney revealed that both kidneys were loaded with staphylococci. The right kidney was treated with silver nitrate, and 8 c.c. of a staphylococcus bacteriophage were introduced through the catheter into the pelvis of the left kidney.

January 20: Specimens showed only a few staphylococci present in the left kidney, with more in the right. Eight cubic centimeters of bacteriophage were introduced into the pelvis of the right kidney.

January 24: We were unable to catheterize the left ureter. Staphylococci still present in the right kidney. Eight cubic centimeters of bacteriophage were again introduced.

January 27: Unable to catheterize the left kidney pelvis. Few staphylococci were obtained from right kidney. Eight cubic centimeters were again introduced.

January 30: Specimens from both kidneys were negative for organisms.

February 15: Specimens were negative for staphylococci. The patient weighed 137 pounds (62.1 kg.).

February 24: Voided specimen contained few cocci.

March 1: The patient's condition was the same as on last examination.

June 12: The patient was feeling well and was entirely relieved of symptoms.

In this case the results should not be emphasized too strongly. Pyelitis frequently clears up of its own accord after removal of stones, as in cases without stone. At no time was there any reaction following the administration of the bacteriophage. No sudoral crisis was observed such as other authors have described.

CASE 2.—*History.*—A. J. W., a laborer, aged 38, entered Dr. M. E. Lott's service on February 10. His family and past history was unimportant. On Nov. 24, 1922, the patient was building a fire escape for a school house and was pulling up the lower section of a balance traceway with a block and tackle when the timber gave way at the top of the building falling four stories, striking his left arm and knocking him from his feet.

Treatment and Course.—He was operated on, and a piece of bone about 4 inches (10.16 cm.) long was removed. The wound was badly infected and discharged profusely, having a bad odor. On February 12, he was operated on a second time at this hospital, and the wire used in the first operation was removed. The wound discharged continuously for two weeks, soaking the dressings so that it was necessary to dress the arm two or three times daily.

February 26: Two and one-half cubic centimeters of staphylococcus bacteriophage were injected into the wound and into the surrounding tissue.

February 27: During the preceding twenty-four hours there had been scarcely any discharge. The same treatment was again instituted.

February 28: The condition was much improved. There was practically no discharge. The same treatment was again given.

February 29: The patient appeared much improved, and the wound was granulating well. Four cubic centimeters of bacteriophage were injected deep into the wound. The treatment was given about 10 o'clock in the morning. At noon the patient had a chill, and 1 o'clock the temperature was 101 F., and the patient was put to bed. The temperature was 104 F., by 2 o'clock; the pulse rate was 120. Blood examination revealed: white blood cells, 19,000; polymorphonuclears, 94 per cent. By 4 o'clock the temperature was down to 102 F., and at 7 o'clock that night it was normal. The patient was up and around the next day, somewhat weak but otherwise as well as usual. The wound was much improved, and there was no discharge.

March 4: The wound was healing, and the patient left the hospital.

The rapid decrease in the amount of discharge following the treatment with the bacteriophage is the interesting fact to be noted. After

Fig. 1 (Case 3).—Healed wound thirty-five days after beginning treatment with bacteriophage.

almost four months of infection, the patient was highly enthusiastic with the results obtained. I do not feel that the reaction described was due to the material injected, but was due rather to the stirring up of the infection (perhaps a pus pocket) deep within the tissues. This is of course to be guarded against when injecting the material into infected wounds, although there appeared to be no resistance to the flow of the material when injected in this case.

CASE 3.—*History.*—L. McN., a negro school boy, aged 14, entered Dr. S. D. Weaver's service on March 20. His family and past history was unimportant. In December, he was carrying some heavy timber and noticed a swelling on

his right forearm. Three days later the swelling ruptured. On March 24, he was operated on, and the bone was curetted. Roentgen-ray examination showed an osteomyelitis with sequestrum formation.

Examination.—Examination on April 2 revealed a wound discharging large amounts of foul-smelling pus. Two cubic centimeters of bacteriophage were given subcutaneously and 2 c.c. were injected into the lesion. The infecting organism proved to be a staphylococcus.

Treatment and Course.—April 3: The lesion appeared to be much better, and there was little pus. The same treatment was again instituted.

April 4: The wound was much improved. There was only one small spot on the dressing where before the dressings were soaked with the discharge.

April 5: One cubic centimeter of bacteriophage was injected into the wound subcutaneously. The wound continued to improve.

April 7: The same treatment was given as on April 5. The wound was healing.

April 11: The wound was healing. There was no discharge. Two cubic centimeters of bacteriophage were given subcutaneously.

April 20: The wound was about one-third its original size. There was no discharge. Two cubic centimeters of bacteriophage was given on dressing.

April 27: Only a narrow area was not healed. There was no discharge. No treatment was given.

May 31: The patient returned and said that his wound had been entirely healed for nearly three weeks.

In this case also the interesting point to note is the marked decrease in the amount of discharge even after the first treatment. It is impossible of course to state whether or not this wound would have healed in six weeks after operation without the bacteriophage treatment. I feel, however, that the treatment with bacteriophage in this case as in the preceding case was directly responsible for the immediate decrease in the amount of discharge, and thus facilitated healing.

CASE 4.—*History*.—F. N., a postal clerk, aged 39, entered Dr. S. Webb's service on March 9. His family history was unimportant. He had had the usual children's diseases. He had had pneumonia ten years before and influenza in 1918. He had had no operations. There was no history of venereal disease. His present illness began three weeks before. He was pitching mail with his right arm into various pigeonholes when he suddenly noticed a sharp pain in his right side under his arm. The pain increased so that he stopped work the next day. The following day he returned to work and worked two days. He said that the pain was getting worse all the time, and it began to pain him when he breathed. He went to bed and put a mustard plaster over his chest and side. The pain became intense, especially on coughing or sneezing, and was located only on his right side and on the anterior surface of his chest. He had had a mild cold for several months.

Examination.—There were several badly decayed teeth and marked pyorrhea. There was a dull area on the right side of the chest extending from the axilla to near the sternum and below the third interspace. A change of level was noticed in lying down and siting up positions. Vocal fremitus was decreased on the right side. Laboratory examination revealed: white blood cells, 17,000; polymorphonuclears 87 per cent. Urinalysis was negative. Fluid from the chest showed a specific gravity of 1.022, 96 per cent. polymorphonuclears, 4 per cent. mononuclears and a large amount of albumin. There were many streptococci in the smear. Roentgen-ray examination showed an abscess in the lower part of the right lung.

Treatment and Course.—March 13: A rib resected and drainage instituted.

March 14: There was considerable drainage with a foul odor.

March 15: The condition was the same.

March 17: The condition was the same. Thirty cubic centimeters of a streptococcus bacteriophage were injected into the cavity.

March 18: There was a large amount of drainage. The odor was not so bad.

March 19: There was a small amount of drainage and hardly any odor.

March 20: Thirty cubic centimeters of bacteriophage were injected into the cavity. There was little discharge and no odor.

March 21: The condition remained the same.

March 22: There was practically no discharge and no odor.

March 23: There was no discharge. Twenty-five cubic centimeters of bacteriophage were injected into the cavity.

March 25: The patient was discharged from the hospital. He said that he "felt fine."

May 15: The patient returned and said that he had felt perfectly well since leaving the hospital.

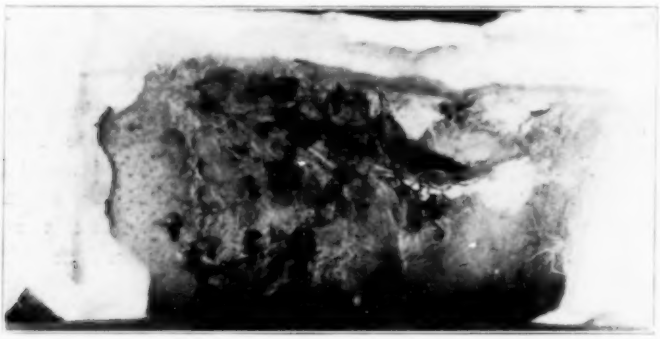

Fig. 2 (Case 5).—Wound on leg April 12, day of second treatment with bacteriophage.

In this case also the effect of the bacteriophage on the character and the amount of the discharge is to be noted. The marked odor so frequently associated with these cases had disappeared in the course of forty-eight hours following the treatment.

Case 5.—*History.*—J. N. C., a sheet metal worker, aged 57, entered Dr. M. E. Lott's service on October 11. His family and past history was unimportant. On October 11, the patient was putting up a water gutter around the roof of a two-story school building when the scaffold fell, and he fell 30 feet to the gound, landing on both feet. He suffered a compound commuted fracture of the right tibia and fibula and a crushing fracture of the os calcis, with dislocation of the astragulus of his left foot.

Treatment and Course.—He was brought to the hospital, and the bones of his right leg were set and the leg put in a plaster cast. The left foot was also put in a plaster cast. On March 26, a piece of bone about 3 inches (7.62 cm.) long was removed from his right leg, and the cast reapplied. The wound was badly infected with *staphylococcus aureus.*

April 10: Two cubic centimeters of staphylococcus bacteriophage were injected into the discharging wound and subcutaneously around the wound.

April 11: The discharge was markedly decreased.

April 12: Two cubic centimeters of bacteriophage were again injected into the wound and subcutaneously around the wound. One cubic centimeter was given subcutaneously into the right arm.

April 13: There was practically no discharge.

April 14: The wound appeared much improved. There was practically no discharge.

April 15: The condition was about the same.

April 16: Two cubic centimeters of bacteriophage were again injected into the wound and subcutaneously around it. Treatment was given at 8 o'clock in the morning. At noon the temperature was 103 F. The patient began to have cramping pains all over the body and marked emesis. Chills were marked and lasted until 5 o'clock that afternoon.

April 17: The patient's condition was a little improved. The wound was healing well. There was no discharge.

April 18: His general condition was much better. His temperature was normal. He had no chills. He had little nausea but felt weak. The wound was healing well.

Fig. 3 (Case 5).—Healed wound on June 2 following treatment with the bacteriophage.

April 23: The patient's condition was good. The wound was healing. There was no discharge. The wound, formerly about 1 inch (2.54 cm.) deep, continued to heal, and on May 18 healing was nearly complete, except for a slight depression which contained a small amount of blood clot.

May 18: The blood clot was cleaned out, and a bacteriophage was placed on the dressing and laid over the wound. The patient had a marked reaction, beginning about 8 o'clock that night, simulating the one described above, only more marked. He was nauseated and had chills and fever for a week, together with marked swelling of the right leg and foot.

June 2: The wound was healed. Roentgen-ray examination showed union of the fractured bones.

The effect on the drainage was as marked in this case as in the cases already described. The reaction in this patient we are inclined to attribute to the protein in the filtrate. This is largely suggested by the second reaction when the material was simply placed on the dressing and applied to the wound, which appeared to be practically healed.

Case 6.—*History.*—Miss E. L. C., a school teacher, aged 27, entered Dr. H. G. Walcott's service on March 9. Her family history was unimportant. The patient had had scarlet fever and whooping cough when a child, with good recovery. Her appendix was removed five years before. She had had influenza in February, 1922. At the end of the school year in 1922, she had had a nervous breakdown. She had had a severe attack of dengue in November, 1922, which lasted three weeks. Her present illness began in April, 1914, with diarrhea and cramping pains in the abdomen, which had lasted until she presented herself. Her stools were watery, but she had not noted any blood. In April, 1922, the diarrhea became more marked, and she had had from six to ten stools a day up to the present time, and more marked during her menstrual period.

Examination of the stool showed the presence of the Flexner dysentery bacillus.

Treatment and Course.—March 12: The patient was given 30 c.c. of bacteriophage lytic for Flexner dysentery by the duodenal tube.

March 13: The patient's stool showed Flexner dysentery.

March 15: The patient had only three stools.

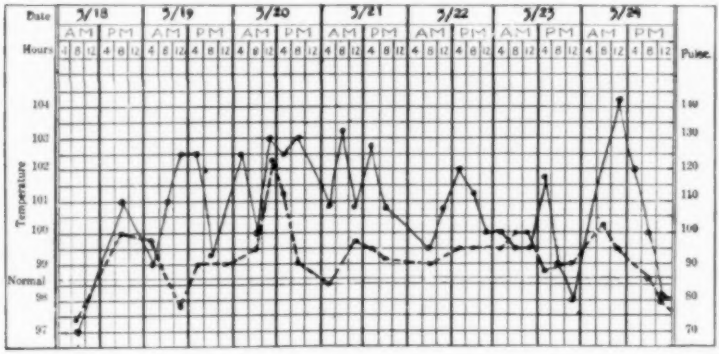

Fig. 4 (Case 5).—Reaction resulting from bacteriophage placed on dressing. The continuous line indicates the temperature, the broken line indicates the respiration.

March 19: Thirty cubic centimeters of bacteriophage were given by the duodenal tube. The patient had three stools. The Flexner bacillus was not recovered from two stools.

March 23: There was one formed stool. The patient had just passed through the menstrual period without diarrhea. The stools had been formed for the preceding four days. The patient was discharged from the outpatient department, and returned home.

May 30: A letter from the patient stated that she had been perfectly well but was again beginning to have diarrhea. She was coming for an examination and further treatment.

Treatment with the bacteriophage relieved this patient of her symptoms within a few days, and she felt perfectly well for more than two months. At no time during the last nine years had she been free from diarrhea, nor had she felt as well as during the last two months.

All other medication failed to give her any relief. According to d'Herelle's theory, this recurrence was due to the organism becoming "refractory" to the bacteriophage.

CASE 7.—*History.*—T. T. E., a laborer, aged 23, entered Dr. M. E. Lott's service on January 28. His family and past history was unimportant. On January 28, he fell from a 43 foot (1307 cm.) derrick and broke both arms and his right leg at the junction of the upper and middle third of the femur. His leg was operated on, January 28, and bone splints were placed. The wound had been discharging large amounts of pus (*Staphylococcus aureus*) for four weeks before he entered the hospital.

Treatment and Course.—February 24: Three cubic centimeters of staphylococcus bacteriophage were injected into the wound and surrounding tissues.

February 25: No improvement was noted.

February 26: The patient's condition was about the same. Three cubic centimeters of bacteriophage were again injected into the wound and surrounding tissues.

February 27: The discharge was markedly decreased.

February 28: Four cubic centimeters of bacteriophage were injected into the wound.

March 4: The wound was healing. One sinus opening was completely healed. There was a slight discharge of clear serum.

March 14: The wound was practically healed. There was no discharge.

While the results in this case were not so immediate or so marked as in the previous cases of similar nature which were treated, the final result, so far as the infection was concerned, was satisfactory. It will be noted that there was no reaction in this patient following the treatments with the bacteriophage.

In addition to the cases we have described above, we have treated two patients with sinus infection both giving a history of nearly four years' duration. One of these patients was operated on two years ago, when the maxillary antrum was opened. He obtained no relief. Both patients complained of a marked greenish foul-smelling nasal discharge and headache. The latter symptom was relieved in one when glasses were prescribed. The other patient obtained no relief. Both patients were given bacteriophage cultures in sterile atomizers, and were told to introduce the material in the usual manner. Both cases have run about the same course following the treatment. A day after treatment there would be a profuse discharge, and then there would be no discharge for from ten days to two weeks, and then it would begin again. After repeated and concentrated treatments, neither case has cleared up entirely although both patients have obtained the temporary relief described. Both patients were medical students. In another student giving a history of a discharging left ear since he was 4 years old following scarlet fever, we have introduced the bacteriophage in 1 c.c. amounts into the ear. The first treatment was given into the ear on May 14, although he had previously received 1 c.c. subcutaneously on

April 30 without benefit. On May 18, the discharge had completely subsided and was still absent on June 5, when the patient left school for his home after the winter term.

In Dr. H. G. Walcott's service, we have treated three patients having a clinical diagnosis of subacute catarrhal cholecystitis. It is interesting to note that in the bile of all these patients *B. pyocyaneus* has been isolated. These patients have been given a stock bacteriophage by duodenal tube in amounts varying from 15 c.c. to 50 c.c. In these cases we have obtained complete relief of symptoms lasting from two to three months, but all of the patients have come back with their former symptoms, although not so marked. At present we are treating a series of children suffering from dysentery by the ingestion method, which will be reported later.

CONCLUSIONS

We have used the bacteriophage in a variety of cases. I believe the time is yet premature to draw elaborate conclusions regarding this method of treating infectious processes; however, it will be seen that in practically all of the cases described we have had some degree of success. The results are encouraging, but I do not feel that they warrant any broad statements at this time. We have administered the bacteriophage subcutaneously, by duodenal tube, into wounds, on dressings, by ureteral catheter, intranasally, intra-aurally and by ingestion in amounts varying from 1 c.c. to 50 c.c. We have had no bad reactions other than in the two cases described in this paper. In a few instances, following the subcutaneous administration little "lumps" have formed under the skin in the subcutaneous tissue, which have been slightly painful but which have quickly disappeared. That the bacteriophage is harmless has been amply proved by the comparatively large amounts which we have given. Indeed in one case Davison gave over 1,300 c.c. without bad effects. These cases are not given as proof of cures, but as observations which lend encouragement for future work with the hope that such work will develop this new weapon for fighting infection, a weapon which holds enormous potential possibilities.

SUBACUTE BACTERIAL ENDOCARDITIS DUE TO A HEMOLYTIC HEMOPHILIC BACILLUS

REPORT OF A CASE *

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NEW YORK

In an extensive literature on the bacteriology of subacute bacterial endocarditis, there has been no mention of the hemolytic hemophilic bacilli. These organisms are closely related to the influenza bacilli, but they differ from them in one important property—their ability to hemolyze red blood cells.

These influenza-like bacilli were first described in 1919 by Pritchett and Stillman,[1] who recovered them from the throats of healthy persons and grouped them under the term "Bacillus X." Rivers,[2] in 1920, suggested that they be considered hemolytic strains of *B. influenzae*. Later in the same year, Stillman and Bourne,[3] defined their cultural characteristics. Walker [4] encountered them in his work on hemolytic streptococcus carriers. Rivers and Leuschner,[5] in 1921, reported on their occurrence in normal throats. They recalled that in 1918, at Fort Sam Houston, members of the Pneumonia Commission had noted hemolytic colonies of gram-negative bacilli in throats of patients with measles. Bloomfield,[6] in 1921, also noted their occurrence in normal persons and in patients with "common colds," in whom, however, he did not regard them as of etiologic significance. In a recent monograph on the hemoglobinophilic bacteria, in which he admirably reviews all the previous work, Kristensen [7] states that he has frequently encountered these bacteria, but only in healthy persons. In his summary, he tabulates, the characteristics distinguishing the hemolytic hemoglobinophilic bacilli from Pfeiffer's bacilli: (*a*) They cause hemolysis. (*b*) They occur only as saprophytes. (*c*) They are less strictly dependent on hemoglobin. (*d*) They may have a coarser morphology. (*e*) They are slightly more difficult to keep in culture.

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* From the Hospital of the Rockefeller Institute for Medical Research, New York.

1. Pritchett, Ida W., and Stillman, Ernest G.: J. Exper. M. **29**:259, 1919.
2. Rivers, T. M.: Bull. Johns Hopkins Hosp. **31**:50, 1920.
3. Stillman, Ernest G., and Bourne, Janet M.: J. Exper. M. **32**:665, 1920.
4. Walker, J. E.: J. Infect. Dis. **27**:618, 1920.
5. Rivers, T. M., and Leuschner, Erida, L.: Bull. Johns Hopkins Hosp. **32**: 130, 1921.
6. Bloomfield, Arthur L.: Bull. Johns Hopkins Hosp. **32**:378, 1921.
7. Kristensen, Martin: Investigations Into the Occurrence and Classification of the Haemoglobinophilic Bacteria, Copenhagen, Levin and Munksgaard, 1922.

We shall record the following case, the first to be reported in which one of this group of organisms has been associated with a fatal pathologic process.

REPORT OF A CASE

History.—G. W., an American school girl, aged 12, was admitted to the Hospital of the Rockefeller Institute for Medical Research on Nov. 8, 1922, complaining of fever. Her family history was negative for rheumatism and heart disease. She had had uncomplicated measles and whooping cough at 3 years of age. For several years she had had periodic attacks of vertigo, preceded by vomiting, which were promptly relieved by lying down. She was usually kept in bed for one or two days following such an attack. In June, 1922 (five months before admission), she had had an attack of nausea and vomiting resembling an ordinary "dizzy spell." On going to bed the symptoms disappeared, and she felt well. Two days later she was taken to her family physician, who diagnosed "heart disease." He informed us that he heard a systolic murmur for the first time on that day, although he had examined her heart many times in preceding years. She was put to bed for two weeks and was seen by her physician several times. She had mild fever for a few days, the highest temperature being 102 F. by mouth. During this period she had no pain, no shortness of breath, no cough and no swelling of the feet. At the end of the attack there was an appreciable pallor, enough to evoke comment by her friends, but in a few weeks her normal color reappeared and she returned to school feeling well in every way. She was able to climb two flights of stairs four times a day without breathlessness, palpitation or fatigue.

On Sept. 25, 1922 (six weeks before admission), an attack began with nausea and vomiting, followed by a severe chill. The following day the only symptoms were slight nausea and anorexia. That day her physician repeated his diagnosis of "heart disease," and from that time observed, at each visit, a mouth temperature of 101 or 102 F. About two weeks before admission she began to have shooting pains in the left knee, without tenderness, pain on motion, or swelling. Later, on one or two occasions, there was observed tenderness over its mesial surface and also a spot of redness, about 4 cm. in diameter, over the patella. There was never tenderness about the hamstrings or popliteal space. From the history, therefore, the existence of a true arthritis seems improbable. On Nov. 1, 1922, she began to cough; the following day her temperature was found to be 103.5 F., and she was thought to be suffering from a mild bronchitis. The cough persisted until admission on November 8.

Physical Examination on Admission.—The patient was a well developed, but poorly nourished girl, pale and not cyanotic. She lay quietly in bed, apparently free from discomfort. The skull and scalp were negative. The eyes were normal; no icterus or petechiae were present. The nose and ears were negative. In the mouth were several decayed teeth. The posterior pharyngeal wall was slightly reddened. The tonsils were not large. On the buccal mucous membrane were three small red spots, less than 1 mm. in diameter, suggestive, but not typical, of petechiae. There were no cranial nerve palsies. The chest was symmetrical; both sides moved equally on respiration.

There was no precordial tenderness or cutaneous hyperalgesia. Area of Cardiac Dulness: In the second space, it extended 2.5 cm. to the right from the midline and 4 cm. to the left; in the third space, 3 cm. to the right and 6 cm. to the left; in the fourth space, 8.5 cm. to the left; in the fifth space stomach tympany was present. The point of maximum impulse was in the fourth space, 6.5 cm. to the left of the midsternal line. At the apex, the first sound was replaced by a high-pitched, musical murmur, which was followed immediately by the second sound. As the stethoscope was moved upward and to the right, the first sound became audible in the third space, just to the left of the sternum. It was followed by a systolic murmur which had a blowing quality in addi-

tion to the musical. Over the aortic area the first sound was distinct, the musical murmur very faint; the second sound was pure. No diastolic murmur was heard anywhere. The rate was rapid; the rhythm regular.

There was no dulness over the lungs. Over the entire lower half of the chest posteriorly, and in the lower axillae on both sides were heard inspiratory and expiratory râles—sonorous, sibilant, and occasionally coarsely crackling. Spoken and whispered voice sounds and tactile fremitus were normal.

There was no tenderness over the abdomen. The edge of the spleen, quite firm, was felt 1 cm. below the costal margin. The liver was not palpable.

A few cervical and axillary superficial lymph glands were felt on each side. There were no palpable epitrochlears.

There was no vaginal discharge.

There was no clubbing of the fingers, no pretibial edema and no petechiae anywhere on the body. The skin everywhere was dry and coarse, in places suggestive of mild ichthyosis. The left knee was slightly red over the patella; there was no tenderness, pain on motion or swelling. The other joints were normal.

The elbow, knee and ankle reflexes were active and equal on both sides. There was a crossed Babinski sign.

The results of blood culture are given in Table 1. The leukocyte count was 16,260. The differential count was: lymphocytes and large mononuclears, 15 per cent.; transitionals, 14 per cent.; polymorphonuclear neutrophils, 68.7 per cent.; polymorphonuclear eosinophils, 1.3 per cent.; unclassified, 1 per cent. The erythrocytes were pale, but otherwise normal.

In the urine was found: a trace of albumin, no sugar, a few red blood cells and a few white blood cells.

The stereoscopic roentgenogram of the chest showed that for a child of her age, the lungs showed rather marked linear shadows extending, fanlike, from the hilus. The apices were clear. There was no indication of pulmonary infarction. The 2-meter plate showed a generalized enlargement of the heart. The transverse diameter was 12.5 cm.; the longitudinal diameter, 13.5 cm. The area of the heart was 101.3 sq. cm. and the angle 40 degrees.

Course of Disease.—On November 9, the general condition was unchanged. The patient was still coughing. She was quite drowsy. Typical petechiae were seen in the morning as follows: one in the left lower conjunctival sac, several on the buccal mucous membrane and one on the chest. There was no sternal tenderness.

In the third interspace just to the left of the sternum the first sound was loud and slapping, resembling that heard in mitral stenosis. In the first space to the left of the sternum was heard a soft, blowing systolic murmur. There were no irregularities in rhythm.

There was no tenderness over the left knee. The distal phalanx of the fourth right toe was tender, but not painful.

Results of blood culture are given in Table 1.

November 10: For the two preceding nights there had been profuse diaphoresis. The preceding night the patient vomited twice, two and one-half and four hours, respectively, after supper, and again on the morning of the tenth, after breakfast. The patient slept only in short naps during the night. In the morning she was sleepy and irritable. There was one petechial spot on the right buccal mucous membrane. The right fourth toe was no longer tender. There was superficial tenderness over the patella of the left knee, with an area of redness about 1 cm. in diameter in its middle. Movement of the joint was painless until it was flexed far enough to make tension on the skin over the patella. The heart sounds were unchanged. There was a small red subcutaneous spot showing through the skin over the palmar surface of the distal phalanx of the right ring finger; it was not tender.

The leukocyte count was 22,400. The differential count was: lymphocytes and large mononuclears, 14.6 per cent.; transitionals, 17.4 per cent.; polymorpho-

nuclear neutrophils, 65 per cent.; polymorphonuclear eosinophils, 1 per cent.; unclassified, 2 per cent. Urinalysis revealed: a trace of albumin, no sugar; a few white blood cells; no red blood cells. She did not vomit after taking 0.3 gm. chlorotone in the morning.

November 11: In spite of sedatives, codein and barbital, she had slept little. The unproductive cough continued. She complained of bilateral frontal headache. There was no tenderness on pressure over the frontal sinuses or antrums. There were two new petechiae in the right conjunctiva and several in the mouth; none could be seen on the skin, but they might readily have been obscured by the hyperkeratosis. Heart: No thrill was palpable. The musical quality of the systolic murmur had changed to a high-pitched, whirring sound, loudest over the third and fourth interspaces just to the left of the sternum, slightly roughened over the pulmonic area. The pulmonic second sound was accentuated. The action was still rapid and regular. The condition of the lungs was the same as on admission.

November 12: The patient slept much during the day, but was restless at night. The only change in her physical condition was an increase in the intensity of the first and second heart sounds, a more forceful precordial impulse and increased redness of the skin over the left patella.

November 13: The patient's condition was unchanged. The results of blood culture are given in Table 1. There were 15,860 leukocytes. The differential count revealed: lymphocytes and large mononuclears, 16 per cent.; transitional cells, 14.7 per cent.; polymorphonuclear neutrophils, 67.1 per cent.; polymorphonuclear eosinophils, 0.6 per cent.; polymorphonuclear basophils, 0.3 per cent.; unclassified, 1.3 per cent. The erythrocytes showed a distinct basophilic stippling and moderate anisocytosis.

November 15: On November 14, 4 gm. of neocinchophen (0.13 gm. per kilogram body weight) were administered by mouth without any effect on the temperature. The only symptom of drug action was increased perspiration, which had been fairly marked every afternoon and evening. On the morning of November 15, the patient looked a little worse—paler. There was one new petechial spot in the mucous membrane of the mouth.

There was less tenderness over the left patella; no new areas of tenderness had developed in the fingers or toes, and none over the sternum or ribs. In the fourth interspace just below the nipple, was heard a murmur which resembled a presystolic crescendo. The rate was very rapid, the rhythm regular. The whirring sound was heard only in the lower precordium. In the pulmonic area the blowing murmur was a trifle louder and rougher than on the preceding day. The results of blood culture are given in Table 1.

Urinalysis revealed: a trace of albumin, a few red blood cells and a few white blood cells.

November 16: On the preceding day the patient received 4 gm. of neocinchophen. It was her birthday, but she showed no interest in gifts or a party which was arranged for her. In the morning of November 16 she looked appreciably worse; the pallor had increased and was extreme. There were no new petechiae. She was clear mentally. Both radial pulses were imperceptible. The only change in the heart murmurs was that the first sound had lost its slapping character. There was dulness over both bases of the lungs with sonorous and sibilant râles. There were no crepitant râles. The reflexes were brisk. The crossed Babinski sign was still present. There was little tenderness over the left patella this morning; the redness had decreased.

The blood film revealed very pale erythrocytes, marked basophilic stippling, moderate anisocytosis and poikilocytosis.

8:30 p. m.: The condition remained unchanged until about 8 p. m., when the attendant noted an alteration in the breathing. A few minutes later the patient was unconscious, and in Biot's respiration; the precordial impulse was imperceptible; the knee reflexes were still present. The Babinski sign was absent. There was no muscular contraction. Respirations continued for several minutes.

The aneurysm of the abdominal aorta, found postmortem, was entirely unsuspected clinically.

Blood Cultures.—Blood from which cultures were to be made was withdrawn from a vein at the bend of the elbow into a graduated syringe, carried to the laboratory and inoculated at once. No anticoagulant was used. The bacteriologic data are tabulated in Table 1. Unless otherwise noted, the cultures were aerobic. All were incubated at 37 C. and examined each day for evidence of growth.

No growth occurred in any of the anaerobic cultures, and growth in the first generation of the aerobic cultures was slow, becoming visible to the naked eye on

TABLE 1.—*Blood Cultures*

Culture Number	Date	Quantity of Blood Inoculated	Medium	Result
W 25	Nov. 8 6: 15 p. m.	Approximately 1.5 c.c.	Dextrose agar plate; after setting the plate was covered with a tubeful of plain agar	5 colonies after 4 days' incubation
		Approximately 1.5 c.c.	Dextrose agar plate; after setting the plate was covered with a tubeful of plain agar	3 colonies after 4 days' incubation
		Approximately 3 c.c.	50 c.c. dextrose broth	Clouding after 2 days' incubation
		Approximately 5 c.c.	150 c.c. dextrose broth	Clouding after 2 days' incubation
W 26	Nov. 9 4: 30 p. m.	Approximately 1 c.c.	Dextrose agar plate	2 colonies after 4 days' incubation
		Approximately 1 c.c.	Dextrose agar plate	No growth
		Approximately 1 c.c.	Plain agar plate	No growth
		Approximately 1.5 c.c.	Dextrose agar deep tube	No growth
		Approximately 1.5 c.c.	50 c.c. dextrose broth	Clouding after 3 days' incubation
		Approximately 3 c.c.	50 c.c. dextrose broth	Clouding after 3 days' incubation
W 30	Nov. 13 11: 30 a. m.	Between 0.5 c.c. and 1.5 c.c.	Dextrose agar plate; after setting covered with a tubeful of dextrose agar	36 colonies after 4 days' incubation
		Between 0.5 c.c. and 1.5 c.c.	Plain agar plate; covered as above	20 colonies after 4 days' incubation
		Between 0.5 c.c. and 1.5 c.c.	Plain agar plate; covered as above	5 colonies after 4 days' incubation
		Between 0.5 c.c. and 1.5 c.c.	3 plain agar plates placed in Brown anaerobic jar; examined on 2d and 7th days	No growth
		2 c.c.	50 c.c. dextrose broth	Granular growth at bottom after 3 days
		4 c.c.	150 c.c. dextrose broth	Granular growth at bottom after 2 days
		3 c.c.	100 c.c. flask dextrose broth filled to the neck, containing piece fresh sterile potato	No growth
		3 c.c.	Same—petrolatum sealed	No growth
W 31	Nov. 15 4: 50 p. m.	1 c.c.	50 c.c. plain agar containing 5 c.c. ascitic fluid—2 large plates poured	No growth
		2 c.c.	50 c.c. plain agar containing 5 c.c. ascitic fluid—2 large plates poured	No growth
		5 c.c.	Added to 85 c.c. distilled water, centrifuged at high speed for 25 minutes; sediment taken up in 3 c.c. dextrose broth; added to 100 c.c. plain agar containing 10 c.c. ascitic fluid; 4 large plates poured	(One plate contaminated by surface spreader); no other growth

the third and fourth days of incubation in dextrose broth and on the fifth day in plates; the plates also showed a distinct increase in the colony count between November 8 and November 13, eight and three days, respectively, before death. In the plates, the colonies were very small, slightly greenish by transmitted light and surrounded by a small zone of clearing. After several transfers, surface colonies on freshly poured blood-agar plates became visible at the end of twenty-four hours. A more detailed study of this organism was made by Dr. Ernest G. Stillman, who reports: "The organism is a small, nonmotile, gram-negative

bacillus which takes the counterstain deeply and exhibits varying degrees of pleomorphism. Some of the rods in eighteen-hour blood broth cultures show definite beading and bipolar staining. Surface colonies after eighteen hours' incubation on rabbit blood agar appear as small, almost pin-point elevations surrounded by a definite zone of true hemolysis. Hemolysis occurs also around the deep colonies. After thirty-six hours they vary from 1 to 2 mm. in diameter, and have an opaque, yellowish center surrounded by a transparent, slightly serrated border. The organism grows readily in blood broth, causing no hemolysis, but producing a dark yellowish green color in the supernatant fluid after a few days. On the other hand, growth is initiated with difficulty in subcultures on blood agar plates. It did not grow on sheep serum agar, ascitic agar, or glucose agar; on oleate agar it grew poorly. In Dunham's peptone solution enriched with 2 per cent blood

TABLE 2.—*Necropsy Cultures, Nov. 17, 1922*

Number	Material	Medium	Result
W 32	About 0.3 c.c. blood withdrawn from right auricle	5 c.c. dextrose broth tube.	No growth.
	1.5 c.c. blood withdrawn from the left ventricle	Dextrose agar plate.....	Many colonies on 3d day—pure culture; same organism recovered from blood during life
	About 1 c.c. blood withdrawn from left ventricle	5 c.c. dextrose broth tube.	Clouding on 4th day—pure culture; same organism
W 33	Pus from sphenoid sinus.	Streaked on freshly poured dextrose blood agar plate	Heavy growth; only one type of colony — pneumococcus, Group 4
	Pus from sphenoid sinus. One loopful.....	5 c.c. dextrose broth.....	No growth

TABLE 3.—*Agglutination*

	Patient's Serum, November 9		Patient's Serum, November 13		Control Normal Human Serum		Broth Control (No Serum)	
Final Serum Dilution	Incubated at 37 C.	Incubated at 55 C.	Incubated at 37 C.	Incubated at 55 C.	Incubated at 37 C.	Incubated at 55 C.	Incubated at 37 C.	Incubated at 55 C.
1: 10	++++	+++	++++	++++	±	±		
1: 20	++++	++++	++++	++++	—	—		
1: 40	++++	++++	+++	++++	—	—		
1: 80	++++	+++	++	+++	—	—		
1: 160	++++	++++	++	+++	—	—		
1: 320	++	++	—	+	—	—		
0							—	—

extract" the growth was luxuriant. Using this as a substrate, acid was produced in glucose, galactose and maltose, but not in levulose, saccharose, lactose or mannite. It did not produce gas. The final hydrogen-ion concentration in Dunham's peptone solution containing glucose and blood extract was p_H 6.2. It did not produce indol. Five-tenths cubic centimeter of an eighteen-hour culture failed to kill white mice and guinea-pigs. In blood broth it remained viable for two weeks at icebox and at room temperature."

This organism can be readily differentiated from such other small, nonmotile, gram-negative bacilli as *B. mallei*, *B. abortus*, *B. melitensis*, *B. pestis* and *B. tularense* by its inability to grow in mediums not containing blood or blood extract. It differs from *B. influenzae*, *B. hemoglobinophilus-canis* and the Ducrey

8. Blood extract was prepared according to the method recommended by Wollstein, Martha J.: J. Exper. M. **30**:555, 1919.

bacillus in being hemolytic. *B. pertussis* and the Morax-Axenfeld bacillus are not true hemophils. The hemolytic hemophilic bacillus, described by Davis,[9] grew much better under anaerobic than under aerobic conditions, and failed to grow at room temperature.

The organism described falls, therefore, into the group of hemolytic hemophilic bacilli. Whether this group should be classified with the influenza bacilli or set apart by itself is an academic question which cannot be dealt with in this paper.

Agglutination.—The organism was agglutinated by the patient's serum in dilutions of 1:160. Serums obtained on November 9 and November 13 were used.

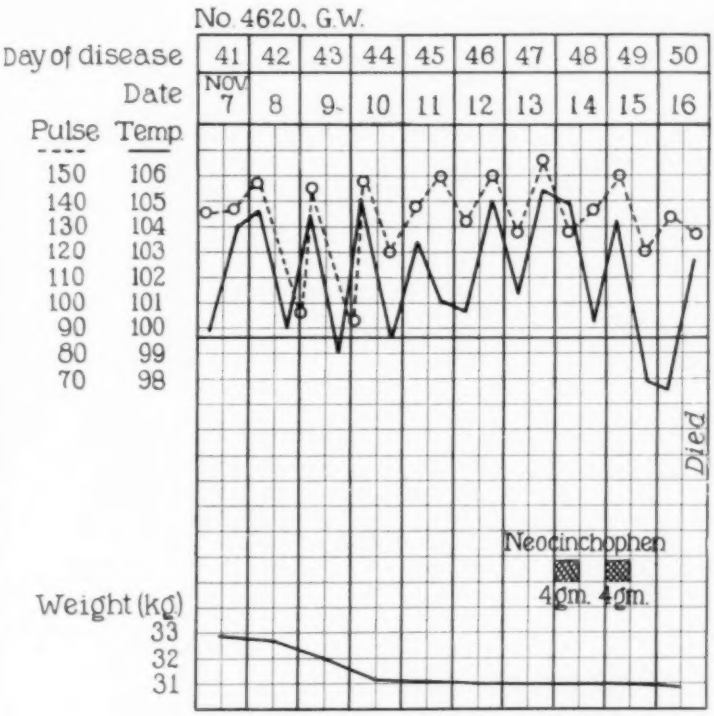

Fig. 1.—Pulse rate and temperature of patient while in hospital.

Technic: A satisfactory suspension of organisms was obtained by resuspending in 20 c.c. of plain broth the centrifuged sediment of a twenty-four-hour blood extract-broth culture (50 c.c. plain broth containing 0.5 c.c. blood extract prepared according to the method recommended by Wollstein).[9] Serum dilutions were made in plain broth; to each 0.5 c.c. of the mixture was added 0.5 c.c. of the suspension of organisms. The agglutinations were made in duplicate, one set incubated at 37 c., the other at 55 C. At the end of three hours they were read, placed in the refrigerator and read again the following morning. Only the final readings are recorded (Table 3).

9. Davis, D. J.: J. Infect. Dis. **7**:599, 1910.

SUMMARY.—A diagnosis of "heart disease" was made in the case of a school girl, 12 years old, who five months before admission to the hospital had an attack of fever lasting two weeks without other symptoms. Three and a half months later she had a second attack of fever with progressive anemia terminating in death on the fiftieth day. She was in the hospital for nine days. There was a systolic murmur of varying quality. Superficial tenderness over one patella; tender finger tips and toes; petechiae in the skin, conjunctiva and oral mucosa

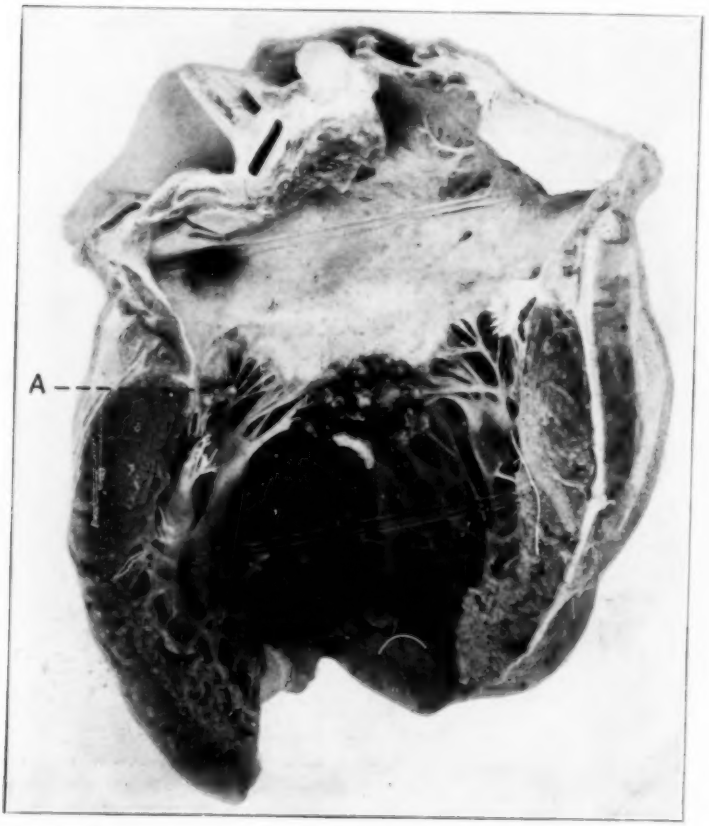

Fig. 2.—The heart opened to expose the mitral valve and vegetation; *A*, the smaller vegetation on the nonaortic cusp with adjacent row of verrucae.

were present. The spleen was palpable. Moderate leukocytosis and low grade hematuria were present. The patient had bacteremia, increasing in intensity during the last week of illness, and a gram-negative hemolytic hemophilic bacillus was isolated. This organism was agglutinated by the patient's serum in 1:160 dilution.

Postmortem Examination.—The anatomic diagnosis was: vegetative and verrucose mitral endocarditis; septicemia (a hemolytic hemophilic bacillus); focal

embolic myocarditis; glomerular nephritis; multiple infarcts of the spleen, kidney and heart; dissecting aneurysm of the abdominal aorta; multiple petechiae in the skin, conjunctivae, buccal mucous membrane, pleurae and meninges; acute localized meningitis; ascites and hydropericardium; bilateral sphenoiditis and ethmoiditis (pneumococcus, Group 4).

There was marked pallor, good physical development and poor nutrition.

The precordial area was small; there were no pleural adhesions. There were a few petechiae on the visceral pleura. The pericardial cavity contained about 60 c.c. of clear, serous fluid; grossly, the pericardium was normal.

The heart weighed 240 gm. The musculature was pale, mottled and nonfriable; the vessels stood out as reddish dots. The left ventricle measured 1.4 cm.,

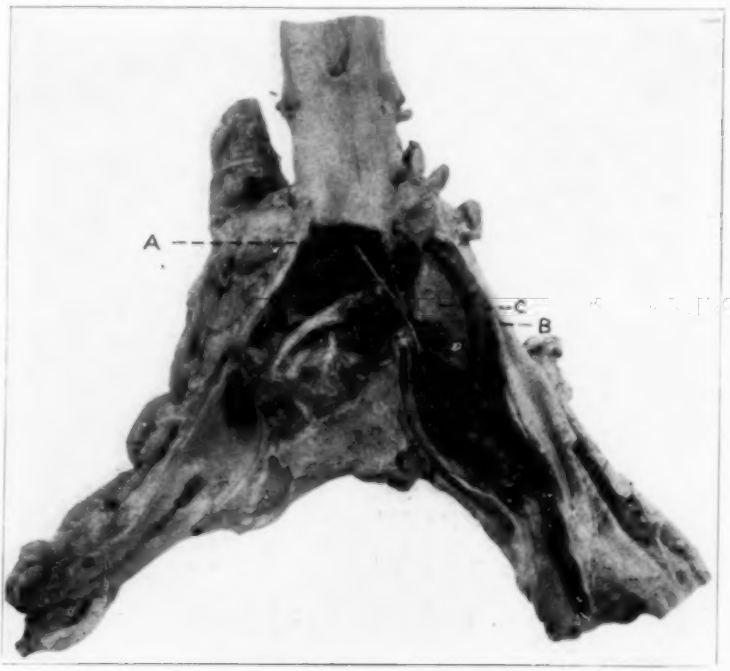

Fig. 3.—The aorta at its bifurcation into the common iliacs; dorsal aspect. *A* indicates the large anuerysmal orifice; *B*, the lumen of the right iliac artery indicated by the straw and encroached on by the aneurysmal contents; *C*, the dissecting aneurysm in the wall of the right common iliac.

the right ventricle 0.4 cm. in thickness. The opened mitral valve measured 8 cm. On the aortic cusp was an irregular, pale, pink vegetation, which measured 2.4 by 1.8 by 1 cm., only slightly friable and firmly attached to the free edge. It involved the chordae tendineae, but did not extend for any appreciable distance onto the auricular surface of the valve. There was a small aperture in the vegetation at its attachment to the valve edge. Elsewhere this cusp showed no gross lesion. On the nonaortic leaflet anteriorly there was a smaller, irregular, tonguelike vegetation measuring 4 mm. in diameter. The remainder of this cusp showed a row of thickly deposited, fairly adherent verrucae along its line of

closure; each was two or three times the diameter of the usual rheumatic verruca. Otherwise the valve did not appear unusually thickened, except for a few small, discrete, yellow plaques at the base of the aortic cusp and under the verrucae. The usual sclerotic thickening commonly seen on its aortic cusp was present, but not accentuated (Fig. 2).

The other valves showed no macroscopic lesions. The larger coronary arteries contained some loose clot; the intima was thin and smooth. The aorta showed fatty streaks throughout its whole length. At its bifurcation into the common

Fig. 4.—The vegetation on the aortic cusp of the mitral valve. *A* indicates the base of the valve; *B*, the vegetation; *C*, the origin of a chorda tendineae. ×7.

iliacs there was an aneurysm on its anterior wall the size of a large walnut. On opening this from behind, a ringlike aperture, 1.5 cm. in diameter, was seen, which connected with the aneurysmal sac and was filled with a red clot. This aneurysm extended down the right iliac, dissecting between the intima and media and re-entering the artery at a point 1.5 cm. below the bifurcation. The aneurysm

bulged into the lumen of the artery, which was considerably narrowed. The anterior wall of the left iliac artery showed a superficial ulceration 1 cm. in diameter just below the aneurysmal orifice (Fig. 3).

The peritoneal cavity contained about 300 c.c. of clear, straw colored fluid. The tip of the spleen extended 2 cm. bellow the left costal margin. The other viscera were normally disposed. The mesenteric glands were moderately enlarged, but on section appeared intact.

The spleen weighed 340 gm. The capsule was adherent to the diaphragm by fine, easily broken adhesions. Its color was brick red, and old and recent infarcts were seen. On section the surface was bright red and firm; the malpighian corpuscles appeared moderately enlarged. There was a yellow, wedge-shaped, fairly firm, infarcted area, 2 cm. in length, at the inferior pole, and more recent, less sharply defined, pinkish yellow infarcts on the anterior border.

The left kidney weighed 165 gm. The capsule stripped readily, leaving a smooth surface, except for large depressions over firm, yellow, infarcted areas. The cut surface was rather pale; the cortical markings were not distinct, but differentiation of cortex and medulla was obvious. Numerous irregular, firm,

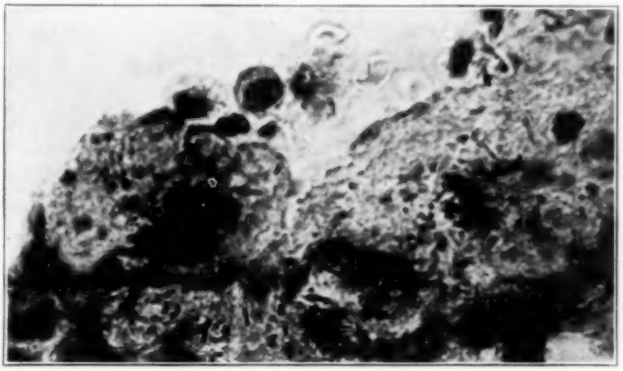

Fig. 5.—A section of the periphery of the vegetation (indicated in Fig. 3) showing the bacilli. × 1,000.

yellow infarcts were seen; one at its inferior pole was almost cartilaginous in consistency, and bright yellow. The right kidney weighed 150 gm. and exhibited the same features.

Both knee joints contained a small amount of clear, viscid material resembling egg white. In the left was seen one small petechia on the synovial membrane between the condyles.

The bone marrow in the femur was abundant, grayish red, moderately soft, and seemed to contain little fat.

The brain appeared edematous and showed a few small petechiae on the lateral surface, and a reddened, suffused area, not definitely outlined on the medial aspect of the right hemisphere.

The internal ears were normal. The sphenoidal and posterior ethmoidal sinuses were filled with about 1 c.c. of very thick, tenacious, greenish gray pus; their exposed lining membrane appeared turbid and reddened. Smears of the pus stained by Gram's and Hiss' capsule stains showed many pus cells and encapsulated, gram-positive, elongated cocci in pairs. No gram-negative organisms were seen after prolonged search. The anterior ethmoidal and the frontal sinuses were normal.

The tonsils were not enlarged; on section they showed no evidence of disease.

Microscopic Examination.—The tissues were fixed in Zenker's solution (with acetic), solution of formaldehyd U.S.P. 10 per cent., Pianese's solution and alcohol. The routine stains were eosin and methylene blue or hemotoxylin and eosin; Giemsa, Gram's, Weigert's elastic tissue, Weigert's fibrin, and Mallory's connective tissue stains were employed where required.

Sections taken from the uninvolved portion of the mitral valve showed nothing of note except a localized fibrous thickening in one area. The earliest small verrucae were formed by a marked localized proliferation of fixed tissue cells,

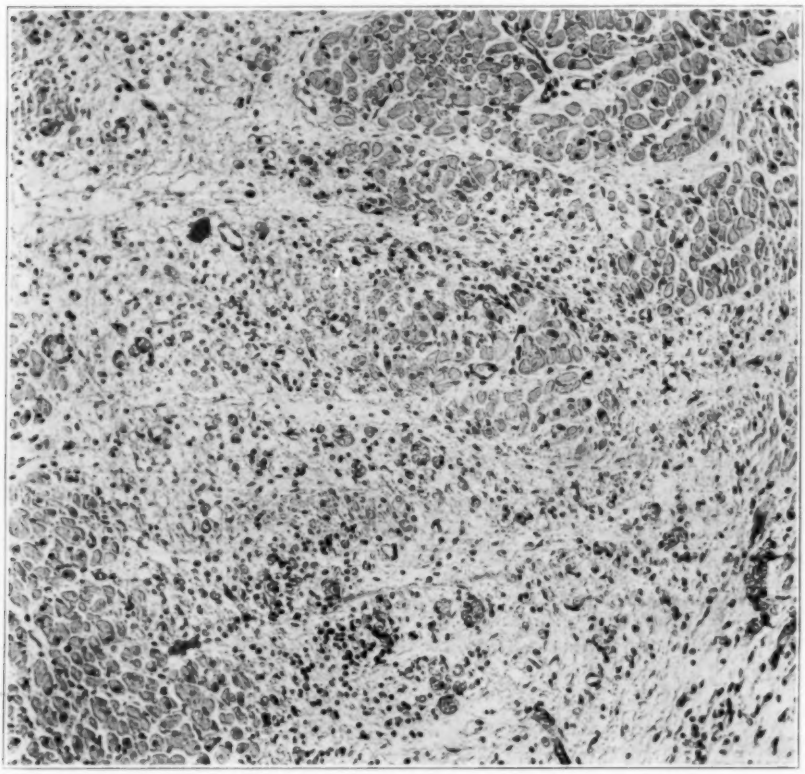

Fig. 6.—An infarcted area in the myocardium of the left ventricle. × 150.

with small fibrinous deposits on the surface, over which the endothelium was missing. Many small vessels were seen in the neighborhood of the verrucae. The large vegetation was attached for a short distance to the free edge and also to the inferior surface of the cusp. A few gram-negative bacilli were noted in the valve itself, and many in the vegetation. At its junction with the valve was an area of active fibroblastic proliferation with few migratory cells (Fig. 4). No vascular thrombi were noted. The vegetation itself was composed of laminated fibrin, débris, red and white blood cells, and masses of bacteria occurring chiefly along the periphery (Fig. 5).

The myocardium was studded with infarcts, some almost the size of a low-power field (Fig. 6); there were also perivascular areas of focal, embolic, exudative myocarditis rich in polymorphonuclear leukocytes. These areas were in close relationship with capillaries and larger vessels which were filled with cellular and fibrinous thrombi containing polymorphonuclear leukocytes in predominance (Fig. 7). The thrombotic process in the same section could be traced in series from the very cellular clot, above described, containing bacteria, to vessels showing a fibrous stenosis. The infarcted areas, however, more numerous than the inflammatory lesions, consisted of edematous tissue in which muscle fibers had disappeared and only the framework remained. The periphery of such areas was being invaded by newly formed capillaries and fibroblasts, and there was some hemorrhagic extravasation; the contiguous muscle fibers were either vacuolated or appeared homogeneous without striations or nuclei. In the remaining unin-

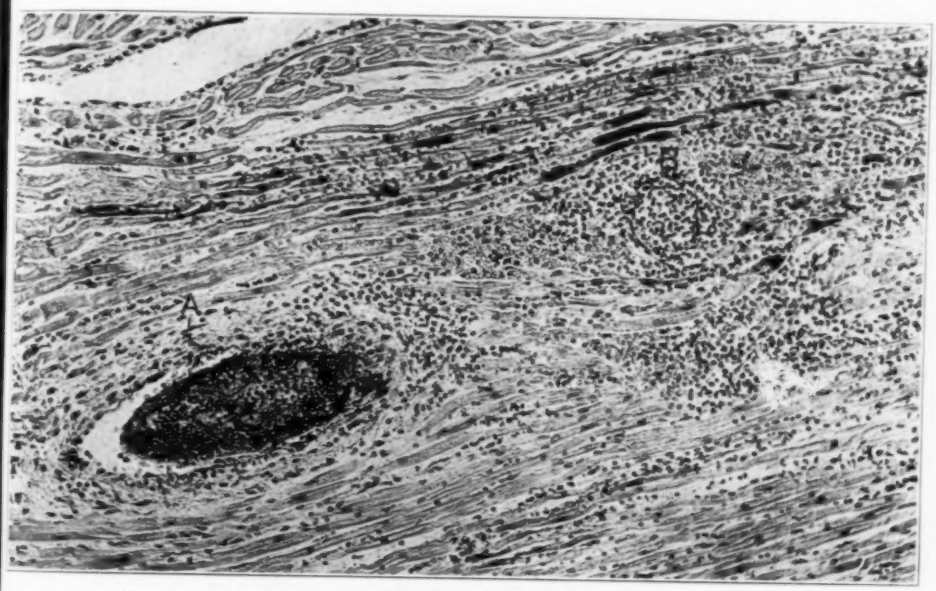

Fig. 7.—Inflammatory process in the myocardium of the left ventricle. *A* indicates a thrombus in the arteriole; *B*, thrombosed capillary; *C*, focal exudative perivascular lesion. × 150.

volved myocardium the fibers were small with distinct striations and normal nuclei.

The pericardium and mural endocardium were intact.

The contents of the aneurysm consisting of cells and débris with little fibrin, lay mostly between the adventitia and media, but in some places broke through the intima to the surface. The intima of the aorta above the lesion was intact, and there were no signs of emboli in the adventitial vessels, while the intima near the aneurysmal orifice was irregularly thickened.

The pulp tissue in the spleen was atrophic throughout, but was invaded by numbers of polymorphonuclear leukocytes; the sinuses were congested. Bland infarcts of irregular size and shape were seen. The malpighian corpuscles were small; their blood vessels were uninvolved, and there were hyaline-like deposits in their centers.

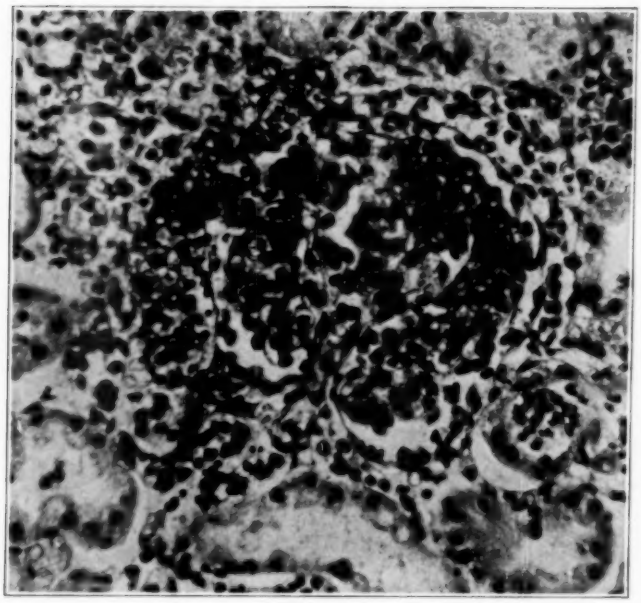

Fig. 8.—Kidney showing the focal glomerulonephritis. × 350.

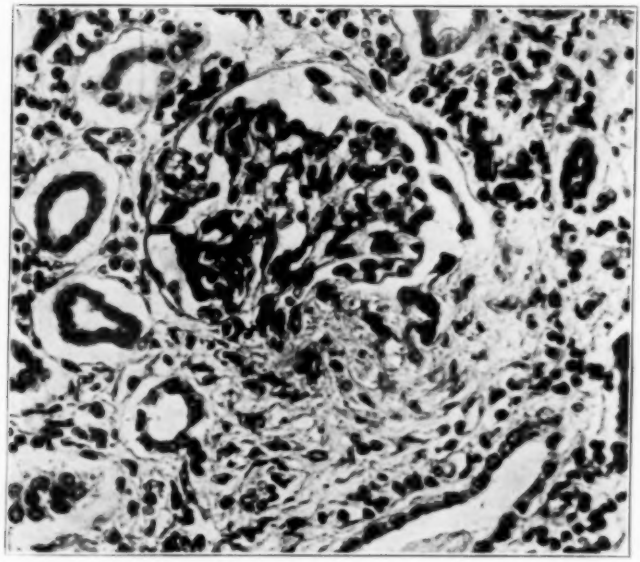

Fig. 9.—Kidney showing the infarction of a segment of a glomerular tuft. × 350.

The tubules of the kidney were comparatively well preserved and contained many cellular casts. Irregular bland infarcts of varying microscopic sizes were seen surrounded by zones of fibrous tissue; the precapillary vessels in the vicinity showed fibrin plugs. Around many of the glomeruli there was an infiltration of polymorphonuclear leukocytes and round cells which extended in some places between the neighboring tubules and in other places involved the whole glomerular tuft. Intertubular infiltration was seen only in the region of inflamed glomeruli (Fig. 8). In certain glomeruli individual capillary loops were plugged with fibrin, while the remaining loops in the same glomerulus appeared normal. A few glomeruli were noted in which a segment of the capillary tuft had undergone hyalinization and fusion with Bowman's capsule (Fig. 9). Complete hyalinization of glomeruli was seen only in or near the larger kidney infarcts.

Tonsils, lymph glands, bone marrow and other organs showed no pathologic lesions.

COMMENT AND SUMMARY

In the case described there was a typical clinical picture of subacute bacterial endocarditis of fifty days' duration. The only illness which might have lead to previous valve injury was a short attack of fever three and a half months before the onset of the final illness. The pathologic picture also closely resembled that described in other forms of subacute bacterial endocarditis. Of particular interest was the presence in the kidney of both types of lesions associated with this disease, namely: (*a*) small infarctions of segments of glomerular tufts, described by Loehlein [10] and by Baehr;[11] and (*b*) a glomerulonephritis. Libman [12] has never found the form lesion in his *B. influenzae* cases, in which glomerulonephritis was frequent.

At necropsy the purulent ethmoidal and sphenoidal sinusitis was the only infective process found which might have antedated the endocarditis and served as a portal of entry; but the pus from the sinuses, in films and cultures revealed no gram-negative bacilli, only pneumocicci (Group 4).

The bacterium recovered from the blood is a member of the family of hemophilic bacilli, differing from influenza bacilli in being hemolytic and comparatively avirulent; in fact, it has never before been reported as occurring in a definitely pathogenic capacity. The proof of its etiologic rôle in this case rests on the following evidence: its isolation in pure culture from the blood on three occasions during life and also at necropsy; the occurrence of morphologically identical bacilli in microscopic sections of the vegetation and of the secondary embolic lesions; and the presence in the patient's serum of specific antibodies (agglutinins) against the organism.

A comparison of this bacterium with its more virulent relative, the influenza bacillus, calls to mind a similar relationship existing between

10. Loehlein: Med. Klin. **6**:374, 1910.
11. Baehr, G.: Am. J. M. Sc. **144**:327, 1912.
12. Libman, E.: Med. Clin. N. America **2**:130 1918-1919.

nonhemolytic streptococci (*Streptococcus viridans*) and hemolytic streptococci. *Streptococcus viridans*, usually less virulent than *Streptococcus hemolyticus*, is the common causative agent in subacute bacterial endocarditis, but also occurs commonly as a saprophyte in the throat, the site from which these hemolytic hemophilic bacilli have heretofore been exclusively recovered.

THE UREA CONCENTRATION FACTOR IN THE ESTIMATION OF RENAL EFFICIENCY*

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Results obtained by the application of the methods now in use in the study of renal function can, at best, show but an approximation of the truth, so far as the efficiency of the kidneys is concerned. The reason for this is obvious. The study of a pathologic reaction is the study of a disturbed physiologic reaction, and the exact physiology of the kidneys is far from perfectly understood. It is now well recognized that what we consider normal anatomic findings are not necessarily associated with normal functional findings, and vice versa. In the absence of certain specific renal stimulants or depressants, and by making the kidney excrete urea to its full capacity, Addis [1] has shown that deductions can be made from functional findings as to the quantity of tissue present. This author and his co-workers [2] have also shown that the kidney substance can excrete seven times the amount of urea ordinarily eliminated. It is therefore reasonable to assume that, normally, in the excretion of urea at least, the kidney tissue is being employed only to the extent of one seventh of its capacity. The general conception of nephritis, as well as of uremia, is undergoing a change from that held before renal efficiency tests became common practice. Some of the clinical signs and symptoms looked on previously as due to anatomic or functional disturbances of the kidney alone are now regarded by many as being due to a general disturbance in metabolism, and associated with, rather than due to, the nephritis. In spite of our incomplete knowledge, however, there is no doubt that the tests now in use have a definite clinical value, if in the interpretation of the results obtained proper consideration is given to the possible sources of technical errors involved in the biochemical analyses and the influence of extrarenal factors.

Practically all methods for determining kidney function now in use are based on the following generalization: When the kidneys become unable to properly excrete the end-products of metabolism, these must either be more slowly excreted than normally or accumulate in the blood, and the degree of retention of these substances in the blood or their rate of excretion in the urine is an index of the degree of impair-

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* From the department of metabolism of the Montreal General Hospital.
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1. Addis, T.: Renal Function and the Amount of Functioning Tissue, Arch. Int. Med. **30**:378 (Sept.) 1922.

2. Addis T.; Sheoky, A. E., and Bevier: Am. J. Physiol. **46**:11 (April) 1918.

ment of renal efficiency. Attempts to give mathematical expression to the estimation of the work done by the kidneys in concentrating substances from the weak dilution in which they are found in the blood to the greater concentration in which they are found in the urine, were first made by Dreser in 1892.[3] Since then the increasing number of factors which influence such calculations have been recognized, and the general consensus of opinion now is that our knowledge of the total work done by the kidneys is still imperfect. Clinically, this is only too well emphasized. In a detailed study of kidney function made in this hospital [4] it was shown that various types of nephritis show various responses to the same test, and therefore no one test for kidney function can be used to the exclusion of all others for the purpose of renal diagnosis.

The biochemical methods in general use for studying the various renal lesions associated with impaired excretion of nitrogenous substances are the Mosenthal modification of the Hedinger and Schlayer renal test meal, the excretion of solids and phenolsulphonephthalein, the estimation of the amount of nonprotein nitrogen in the blood, including urea, uric acid and creatinin, and the urea concentration test of MacLean and de Wesselow.[5] The technical difficulties previously encountered in these tests have been practically eliminated by improved biochemical methods. In all these tests the interpretation of the results is complicated by extrarenal factors. The possible influence of such factors in the renal test meal have been pointed out by Mosenthal in his original [6] and in subsequent articles. In the study of the excretion of solids, the methods generally employed include the determination of the specific gravity of the urine. That the specific gravity is no real quantitative index of the total concentration of solids has been known by physical chemists for a long time. Judging from the general application of the specific gravity in estimating solids, this is, however, not generally recognized clinically. Two solutions, one containing urea and the other salt or sugar, and each having the same number of grams per liter, will not have the same specific gravity. Recently this has been given clinical consideration.[7] In the common method of studying the

3. Dreser, in Cushny, A. R.: Monograph on Physiology. The Secretion of Urine, New York, Longmans, Green & Company, 1917. Lea & Febiger.

4. Rabinowitch, I. M.: A Study of the Urea Concentration Test for Kidney Function, Arch. Int. Med. **28**:627 (Dec.) 1921.

5. MacLean, H., and de Wesselow, O. L. V.: On the Testing of Renal Efficiency with Observations on the Urea Coefficient, Brit. J. Exper. Path. **1**:53 (Feb.) 1920.

6. Mosenthal, H. O.: Renal Function as Measured by the Elimination of Fluid Salt and Nitrogen and the Specific Gravity of the Urine, Arch. Int. Med. **16**:733 (Nov.) 1916.

7. Addis, T., and Foster, M. G.: The Specific Gravity of the Urine, Arch. Int. Med. **30**:555 (Nov.) 1922.

excretion of solids [8] this is indirectly recognized by accepting the data obtained only when associated with a definite diet. Other factors than renal which may frequently cause an increase in the amount of non-protein nitrogenous constituents of the blood have been pointed out. These include acute pancreatitis, general peritonitis, intestinal obstruction [9] and lethargic encephalitis.[10] Even where the retention of nitrogen is due to renal disorder alone, the correlation of the clinical picture with the laboratory data is of importance in distinguishing between temporary and permanent disturbances. In many urologic conditions associated with retention of urine, the prognostic significance of the renal function tests can only be appreciated by estimating the relative importance of extrarenal and renal factors.[11] The possible sources of error in the interpretation of the results of the urea (urine) concentration test have been pointed out by the authors of the test.[8] The writer has shown the effects of delayed absorption of urea from the alimentary tract.[4] What has probably not been sufficiently emphasized is the necessity of performing the test under standard conditions. Many results not consistent with the clinical picture were frequently encountered in this hospital before standard conditions were adopted. This routine is employed: The patient is allowed no food or fluids of any kind after 6 p. m. the evening before the test. At 6 a. m. on the day of the test the patient voids. This specimen is discarded. The urea is then given as described by the authors of the test, and the urine is collected at 7 a. m. and 8 a. m. The performance of the test in this manner interferes least with the patient's comfort, conforms best to the hospital routine, does not interfere with meal hours, and at the same time avoids the possibility of the patient receiving any food or drink preliminary to the test. The necessary precautions described by the authors of the test, discarding tests which produce diuresis, etc., are strictly observed.

When the renal lesion is associated with an impairment in the excretion of nitrogenous substances the application of urea studies in the estimation of renal efficiency probably, as the data here show, excels all other methods. A consideration of some of the aspects of our present knowledge of urea metabolism well emphasizes this point of view. Urea is a normal end-product of protein metabolism and in the

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8. Sharlit, H., and Lyle, W. G.: A New Method of Interpretation of the Renal Function Test Meal, Arch. Int. Med. **28**:649 (Nov.) 1921.

9. Rabinowitch, I. M.: The Prognostic Value of the Study of the Blood Chemistry in the Acute Abdomen, J. Canadian M. A., March, 1921.

10. Umber, F.: Mesencephalitis epidemics, Deutsch. med. Wchnschr. **47**:261, 1922.

11. Rabinowitch, I. M.: The Prognostic Value of the Study of the Blood Creatinine in Nephritis, J. Canadian M. A. May, 1921.

average adult on an average diet constitutes about 80 to 90 per cent. of the total nitrogen eliminated in the urine in twenty-four hours. Unlike some other urinary constituents, a great deal of work must be done by the kidney in excreting urea. The energy used by the kidney in excreting urea can be calculated according to known physical principles by applying the Vant Hoff theory of solutions. Further proof of the great amount of work the kidney must do to excrete urea is furnished by the experiments of Barcroft and Straub on the oxygen consumption of the kidney in relation to diuresis. There is a marked contrast between these results and those obtained with the diuresis due to Ringer's solution, water or sodium chlorid. Urea is uniformly distributed in all the organs and body tissues, including the blood.[12] An appreciation of this fact is important. The uniform diffusion of urea prevents osmotic pressure differences across the membranes of the body. This absence of osmotic pressure differences will therefore not influence the movement of the body fluids and therefore will be less likely to cause hydremia,[3] which is an important factor influencing renal excretion. Following the administration of urea it undergoes no chemical change, and normally its rate of elimination is rapid. When prevented from being excreted, it is all stored in the body, except traces which appear in the bile and sweat. Its rate of excretion is governed by its concentration in the blood. Diuresis following urea administration is due to kidney activity alone. Large amounts may be injected and followed by considerable diuresis, yet there may be no increase in the blood flow through the kidney. This is demonstrated in one of the experiments by Lamy and Mayers.[13] Besides the excretion of urea being chiefly a function of the kidneys, extrarenal factors causing high blood ureas or low urine urea concentrations are more easily excluded than factors which influence the other tests. The most common urea tests employed are: (*a*) the estimation of the blood urea nitrogen; (*b*) the urine urea concentration test of MacLean and de Wesselow, and (*c*) Addis' ratio $\frac{\text{Urea in one hour's urine}}{\text{Urea in 100 c.c. blood}}$

THE UREA CONCENTRATION FACTOR

That the function of the kidneys can be gaged approximately by the association of blood and urine studies has been recognized for a long time. The earliest attempt to do this has been by the application of the freezing point (Δ) studies to blood and urine. In 1921, MacLean[14] reported the principle of dividing the urine urea by the

12. Marshall, E. K., and Davis, D. M.: Urea. Its Distribution and Elimination from the Body, J. Biol. Chem. **18**:53, 1914.

13. Lamy and Mayers, quoted from Cushny: J. Physiol & Path. **8**:258, 1906.

14. MacLean, H.: Discussion on Renal Efficiency Tests, Brit. M. J. **2**:245, 1921.

blood urea, but, as Harrison [15] pointed out, "did not definitely advocate the simple expedient of combining the two tests and thus simultaneously checking the urea concentration (urine) and standardizing the blood urea." Unfortunately, Harrison, as he himself states, in applying this principle, was unable to give normal values. Harrison accepted normal urea concentration factor values from a study of all patients having a urine urea concentration of over 2 per cent. The urea concentration factor $\frac{\text{mg. urea per 100 c.c. urine}}{\text{mg. urea per 100 c.c. blood}}$ shows that such findings do not necessarily indicate a normal efficiency of the kidney. Accepting as normal a urine urea concentration of 2 per cent. or over, when found two and one half hours after the ingestion of 15 gm. urea, the lowest blood urea concentration at this period was 37 mg. and the highest 133 mg. per 100 c.c. The normal values of the urea concentration factor were: lowest, 18 mg., and highest, 72 mg. The maximum increase in the concentration of blood urea over that present before administration of urea was 58 mg. Analysis of all these data shows that in only one case could the patient be regarded as free from any renal lesion—that in which the urea concentration factor was 72. The other data quoted above were obtained from patients having lesions, including chronic nephritis, calculus of the right kidney and unilateral malignant tumor of the kidney. Qualitatively, the results obtained, however, had definite significance.

The data recorded in this hospital are based on the study of 200 cases, in all of which there were renal lesions associated with ozotemia or other evidence of a disturbance in the excretion of nitrogenous substances. A study was made of the value of the estimation of the urea concentration factor as a test for renal efficiency as compared with the other test commonly in use.

Technic.—In all the urea estimations of the blood and, with only few exceptions of the urine, the Van Slyke urease method was used. In the few instances in which the hypobromite principle was applied, the Stehle [16] method was used with the Van Slyke carbon dioxid apparatus. A possible source of error in the urease method which appears to be worth recording is the fact that at times the activity of the urease preparation may be impaired, thus yielding low urea values. All urea determinations should be carried out in duplicate, and the activity of the urease constantly gaged by a control consisting of a urea solution of known concentration. When protein is present in the urine in excess of 0.4 per cent., this should be removed where the hypobromite principle is applied. Harrison describes a simple procedure for this purpose with the use of salicyl-sulphonic acid.

A great advantage of urea estimations over the various dye tests is that pus, blood, bacteria and urinary pigments do not interfere with the results.

15. Harrison, G. A.: On Urea Tests of Renal Function, Brit. J. Exper. Path. **3**:28 (Feb.) 1922.

16. Stehle, R. L.: The Gasometric Determination of Urea in Urine, J. Biol. Chem. **47**:13, 1921.

In order to have a more accurate idea of normal values, a series of observations were made on persons having no albuminuria, a normal blood urea nitrogen and clinically being normal, with the exception of mild surgical lesions, lacerated hands, preoperative hernias, etc. The following routine was adopted and strictly adhered to. All subjects were hospital ward cases and could thus be kept from factors influencing the test, food, fluids, etc. No food or fluids of any kind were allowed after 6 p. m., the day before the test, and the usual procedure followed as described with the urea concentration test above. A specimen of blood was also obtained prior to the administration of the urea.

The data thus obtained were: (*a*) blood urea before the administration of urea, (*b*) blood urea two hours after administration of urea, (*c*) urine urea concentration one hour and two hours after giving urea, and (*d*) urea concentration factor $\frac{\text{Mg. urine urea per 100 c.c.}}{\text{Mg. blood urea per 100 c.c.}}$

TABLE 1.—*Normal Data*

		Mg. Per 100 C.c.
Blood urea nitrogen (before giving urea)	Lowest	13
	Highest	21
	Mean of all values	18
Blood urea nitrogen (after giving urea)	Lowest (increase)	2
	Highest (increase)	20
	Mean of all values	9
		Per Cent.
Urea concentration (urine) after 15 g. urea	Mean of all values	2.38
	Lowest	1.64
	Highest	3.86
Urea concentration factor	Lowest	29.6
	Highest	81.3
	Mean of all values	41.1

TABLE 2.—*Results of Two Hundred Cases*

	Number of Cases	Per Cent. of Total
Subnormal urea concentration factor	167	83.5
Increased blood urea nitrogen	140	70.0
Subnormal urine urea concentration	113	56.5
Types of Cases		
Normal blood urea (upper limit) and normal urine urea concentration (lower limit)	22	11.0
Normal blood urea and low urine urea concentration	26	13.0
Increased blood urea and normal urea concentration	65	32.5
Increased blood urea and diminished urine urea concentration	87	43.5
Normal urea concentration factor	33	16.5
Normal urea concentration factor in the presence of a normal blood urea or urine urea concentration	6	3.0

All blood urea values are recorded in terms of mg. urea nitrogen. Comparing our normal data as shown in the Table 1 with those of Harrison's quoted above, it will be noted that the urea concentration factor was greater, both in the lowest and highest findings, the maximum blood urea concentration following the ingestion of urea was less, and the increase in the blood urea after ingestion or urea over that found before ingestion was also less. From a consideration of these data and the clinical picture of the subjects, it is apparent that these data and clinical pictures of the subjects more closely approximate normal values. The fact that these data were obtained half an hour earlier than those of Harrison's after giving the urea can have little bearing on the results, since both Harrison's and these data show that in the majority of cases the maximum urine urea concentration is reached at the end of the second hour. It is therefore reasonable to assume that at this period the blood will be found to have the maximum amount of urea, since the amount of urea in the blood governs the rate of excretion.

DISCUSSION OF RESULTS

Albuminuria still remains the most frequent and certain sign of kidney lesions. It appears reasonable to assume that in the great majority of the cases studied—in all of which the patient had albuminuria—there must have been some functional changes. Since,

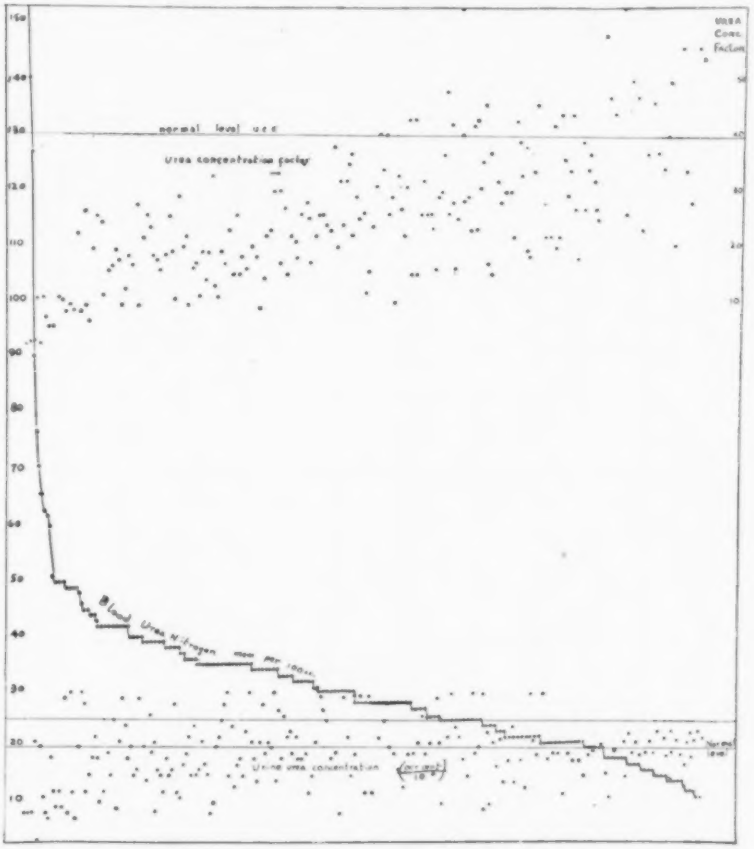

Chart 1.—Blood urea nitrogen and urea concentration factor as determined in 200 normal cases.

however, the kidneys have an enormous amount of reserve capacity, disturbances in function will not be noted until only the minimum essential functioning tissue is left. The most sensitive test should be the one which shows a functional disturbance in the greatest number of such cases. It will be noted in Table 2 that the urea concentration

TABLE 3.—*Results of Two Hundred Cases*

Record No.	Blood: Urea Nitrogen, Mg. per 100 C.c.		Urine: Urea Concentration, per Cent.		Urea Concentration Factor	Record No.	Blood: Urea Nitrogen, Mg. per 100 C.c.		Urine: Urea Concentration, per Cent.		Urea Concentration Factor
	After Urea	Before Urea	First Hour	Second Hour			Before Urea	After Urea	First Hour	Second Hour	
381	162	154	....	0.84	2.4	504	42	53	2.04	2.22	19.5
1703-1	146	140	1.20	0.84	2.6	1086	42	49	1.47	1.87	17.7
1631	140	127	0.76	0.80	2.6	1083	42	50	1.02	1.02	9.5
122	95	90	1.98	2.10	10.3	45	42	46	0.96	1.20	....
1814	79	77	0.43	0.36	2.1	472	42	49	2.04	1.92	12.1
1149	86	71	1.41	2.00	10.8	366	42	43	....	1.53	18.3
314	69	66	0.26	1.14	7.6	331	42	44	2.40	2.56	16.6
270	72	63	0.78	0.86	5.5	456	42	48	1.14	0.96	27.2
1027	70	62	0.72	0.78	5.2	1296	42	46	1.44	2.16	9.3
1916-1	76	60	1.78	1.80	11.1	136	40	50	3.00	2.90	21.9
1024	59	51	1.44	1.38	10.9	471	40	48	2.40	2.40	27.1
649	56	56	0.80	0.96	8.0	24	40	47	1.68	1.85	23.3
379	60	50	....	1.26	9.6	709	40	58	1.80	2.00	18.3
357	54	50	0.90	0.96	8.3	312	39	46	1.80	1.56	17.6
2011-1	55	49	2.76	2.91	22.8	2117	39	43	1.98	1.68	15.8
1812	54	49	0.93	0.88	7.6	2247	39	54	3.00	2.90	18.2
691	53	49	2.76	3.00	26.5	1381	39	49	1.70	2.04	25.1
904	61	49	0.96	1.28	9.6	1085	39	57	1.64	1.41	19.4
1736	53	48	1.64	0.72	6.3	1084	39	42	2.88	2.60	11.5
315	49	46	2.28	2.08	19.6	315	38	47	1.86	1.98	29.0
716	54	45	2.94	3.00	25.8	688	38	46	2.40	2.18	19.7
134	55	45	2.40	2.88	24.4	967	38	43	1.14	0.80	22.1
2354	49	44	1.20	....	11.4	551	38	48	1.32	1.68	8.6
26	47	44	1.50	1.56	15.5	1066	37	43	1.82	1.59	16.3
2288	52	43	1.80	1.86	16.7	311	37	49	1.32	1.20	17.2
....	....	....	....	....	....	....	....	....	....	....	11.4
1739	36	46	1.02	1.83	18.6	1582	34	40	1.50	1.30	15.1
779	36	43	1.54	1.54	13.8	549	34	37	1.82	1.74	21.8
2661	36	42	2.10	1.68	18.7	522	34	39	1.76	1.80	21.5
540	36	40	2.64	2.82	32.9	1161	33	40	1.74	1.51	17.6
1094	35	43	1.20	1.20	13.0	725	33	42	2.53	2.38	26.5
1112	35	47	1.16	1.12	11.0	500	33	40	3.00	3.00	35.0
1310	35	42	1.46	1.71	19.0	1874	33	36	2.10	2.16	28.0
968	35	50	1.72	1.87	17.4	1738	32	35	1.92	1.86	24.8
894	35	46	2.20	2.28	23.1	1775	32	39	1.40	1.40	16.7
807	35	46	1.26	1.50	15.2	2061	32	37	1.70	2.10	20.6
764	35	43	2.16	2.40	26.0	1129	32	36	2.60	2.80	26.5
163	35	47	1.44	1.50	14.9	959	32	34	1.88	1.92	26.4
627	35	43	1.50	1.68	18.2	2645	32	42	1.92	2.16	24.0
1572	35	47	0.60	2.16	16.0	1506	31	40	1.80	2.04	23.5
1780	35	39	0.66	1.70	30.2	2193	31	37	3.00	3.00	37.9
2240	35	41	1.62	1.56	18.0	1875	30	34	0.66	1.44	19.8
434	35	40	2.40	0.74	8.6	1360	30	40	1.84	2.75	32.1
581	35	36	0.96	1.68	14.0	1207	30	36	1.92	1.88	24.4
2651	35	42	1.98	2.01	22.3	626	30	38	2.24	2.60	31.8
2560	35	44	2.20	2.30	23.3	2526	30	32	1.92	2.28	35.3
1374	34	40	0.83	2.50	20.6	228	30	41	2.34	2.38	27.1
1278	34	39	3.00	2.80	33.5	25	30	40	1.80	1.92	22.4
1113	34	46	2.01	3.00	30.4	523	30	36	2.10	2.20	28.6
648	34	42	1.68	1.56	17.3	211	30	33	1.56	1.80	25.4
2353	34	41	2.00	2.40	27.3	674	30	33	1.65	1.82	26.5
2102	29	30	....	0.96	12.4	1206	25	32	1.50	1.96	29.7
999	28	38	1.20	1.29	15.8	1280	25	27	1.59	2.12	36.8
117.	28	30	1.92	1.56	24.4	1358	25	36	1.42	2.10	48.5
1246	28	34	1.50	2.17	30.7	960	25	35	1.76	1.92	26.2
1270	28	35	3.00	....	40.0	908	25	36	2.04	2.10	42.5
1401	28	36	1.40	2.70	34.5	870	25	39	1.56	1.68	28.5
1128	28	30	2.42	2.60	40.5	671	25	33	3.00	3.00	15.8
1125	28	33	1.44	1.88	26.3	613	25	37	2.16	2.16	25.7
843	28	31	1.80	1.92	28.6	2273	25	32	1.56	1.08	63.4
582	28	40	0.78	0.84	9.8	1774	25	40	1.70	2.30	40.0
435	28	42	2.82	3.00	33.4	1163	18	22	3.00	3.00	28.0
348	28	39	2.52	2.28	27.3	1307	24	28	2.18	2.40	29.0
28	28	35	1.50	1.52	21.6	2320	24	30	1.80	2.30	22.6
2413	28	29	1.76	1.98	31.0	1815	24	30	0.99	1.89	42.5
2351	28	32	2.64	3.00	43.5	1596	24	33	0.37	1.50	22.6
1583	28	36	0.84	1.20	15.5	1057	23	33	2.58	3.00	43.2
1123	27	32	2.54	3.00	43.5	555	23	30	2.16	1.96	30.7
31	27	40	1.22	1.20	14.6	2067	23	26	1.90	2.04	36.2
2194	27	39	1.50	2.20	26.3	1187	22	30	3.00	....	46.2
1869	27	37	2.25	2.50	31.6	873	22	27	0.90	0.96	16.6
961	26	38	1.88	2.04	25.6	2481	22	29	2.34	2.36	38.2

TABLE 3.—*Results of Two Hundred Cases—(Continued)*

Record No.	Blood: Urea Nitrogen, Mg. per 100 C.c.		Urine: Urea Concentration, per Cent.		Urea Concentration Factor	Record No.	Blood: Urea Nitrogen, Mg. per 100 C.c.		Urine: Urea Concentration, per Cent.		Urea Concentration Factor
	After Urea	Before Urea	First Hour	Second Hour			Before Urea	After Urea	First Hour	Second Hour	
958	25	36	1.64	1.98	25.7	2187	22	36	1.20	1.00	13.2
868	26	34	1.30	1.68	23.2	2044	22	32	2.46	2.18	31.6
29	26	41	1.26	1.32	15.6	2030	22	29	1.72	1.70	27.6
960	25	31	1.76	1.92	28.6	1961	22	34	2.14	2.20	30.2
1589	22	30	1.18	2.10	30.2	1662	18	28	1.56	1.48	24.6
1581	22	26	0.84	1.20	21,7	11-1	18	26	1.80	1.86	33.6
1030	21	32	2.86	3.00	43.2	2168	17	30	2.20	2.40	37.3
842	21	29	2.04	2.40	38.6	1970	17	22	1.22	1.49	31.6
771	21	28	2.08	1.98	33.0	1900	17	29	1.68	1.70	27.4
261	21	36	1.32	1.44	18.6	9-1	17	28	1.63	1.49	24.8
63	31	34	3.00	2.76	37.6	98	16	24	....	3.00	58.4
2589	21	29	0.96	1.08	17.6	2267	16	22	2.04	2.22	47.2
2514	21	38	3.00	....	36.7	1548	16	20	1.80	1.90	44.1
2180	21	33	2.12	2.40	33.7	8-1	16	22	3.00	3.00	63.0
2164	21	27	3.00	2.70	46.2	226	15	26	1.26	1.48	26.6
2108	21	35	1.44	1.68	22.6	2417	15	18	2.08	1.96	50.9
1853	21	24	0.66	1.10	21.7	1550	15	19	1.30	1.90	46.7
1823	21	29	1.02	1.34	21.7	1535	15	24	0.84	1.20	23.3
2511	20	34	3.00	....	41.7	1536	14	23	1.98	1.90	37.4
2091	20	36	1.56	1.56	20.2	5-1	14	19	1.92	1.86	45.8
1186	20	32	1.58	1.56	22.4	30	14	24	1.08	1.85	36.6
1714	20	29	2.04	2.76	44.5	2000	14	22	2.31	1.59	33.6
1648	20	27	2.22	2.06	35.7	1571	14	23	1.80	1.96	39.6
1607	29	30	1.56	1.83	28.6	3-1	13	19	2.28	2.04	50.0
2041	19	28	1.20	2.04	34.0	1714	12	22	2.04	0.96	20.4
1549	19	32	2.80	3.00	43.6	1552	12	18	2.52	2.16	56.1
2046	18	29	1.50	1.70	27.4	2-1	12	24	2.13	1.76	34.3
1909	18	26	0.74	1.00	17.6	1561	11	20	....	1.20	28.0
1964	18	25	2.00	2.10	39.6	1-1	11	17	....	2.02	55.6

factor was the most sensitive test, the blood urea the next and the urine urea concentration the least. If one considers the factors which influence the results of the urea concentration factor, the fallacy of depending on the blood urea alone or on the urine urea concentration alone is obvious. The earliest evidence of impairment in renal efficiency may be but a slight inability to concentrate. During the day the kidneys may, however, completely remove all the waste products formed, and therefore the blood urea concentration will be normal. Since the amount of urea in the blood governs the rate of urine urea excretion, a high blood urea may at times be associated with a normal or nearly normal urine urea concentration. Therefore the fallacy of depending on the urine urea concentration alone also becomes obvious. In either of these instances, as shown in Table 3, the urea concentration factor shows impairment. This test failed in only six cases out of the total 200 studied.

In fifty other cases previously studied the necessary data for the determination of the urea concentration factor were obtained but were not then considered from this point of view. An added interest lies in the results obtained in these cases in that in all of them the phenolsulphonephthalein test was made. It is generally recognized that remarkable fluctuations may at times occur in the dye excreted, leading

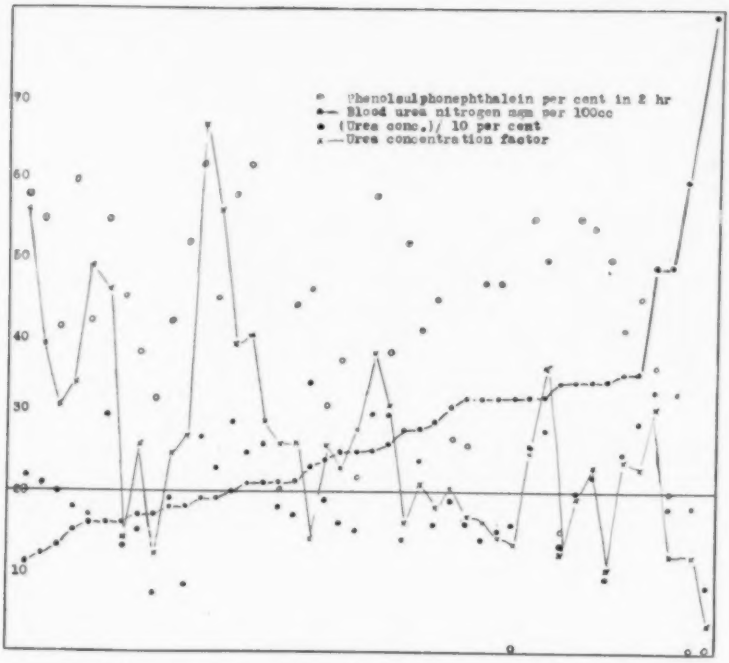

Chart 2.—Blood urea concentration from normal to high values.

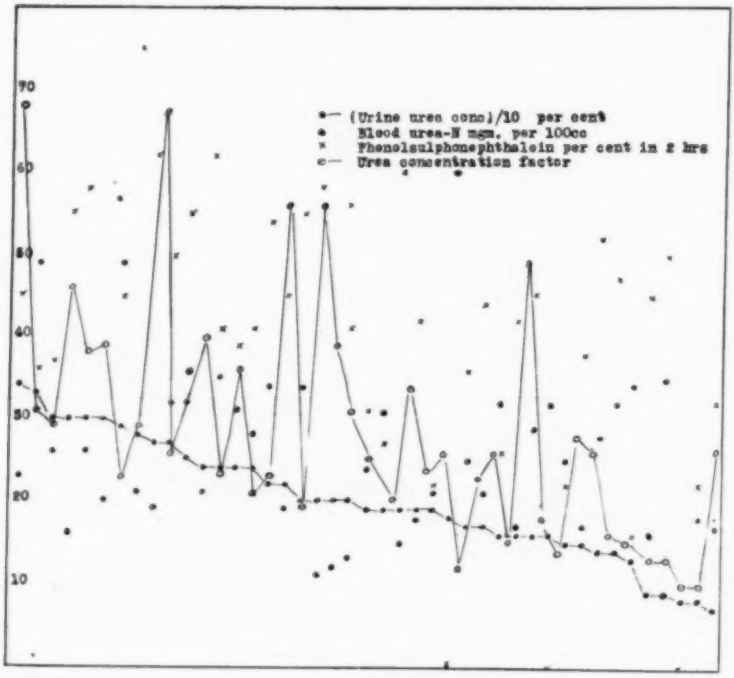

Chart 3.—Urine urea concentration variations from normal to low values.

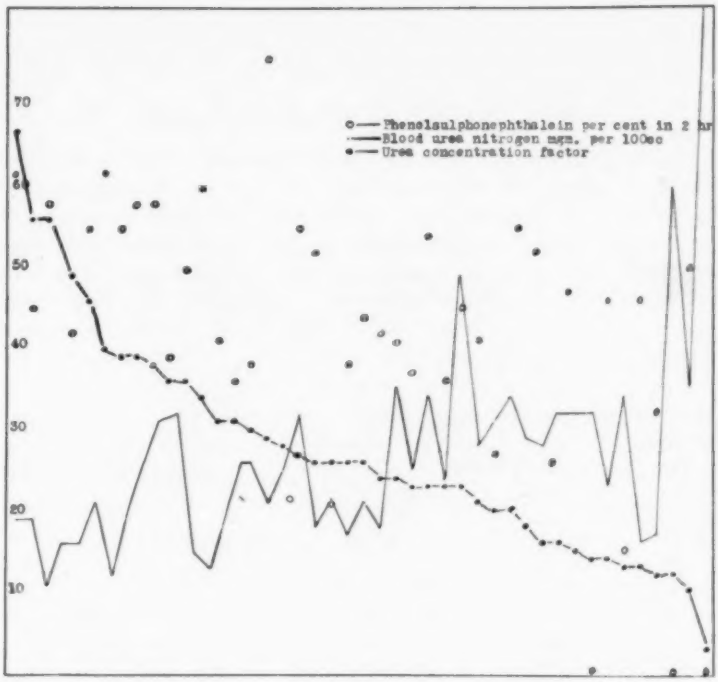

Chart 4.—Urea concentration factor from normal to low values.

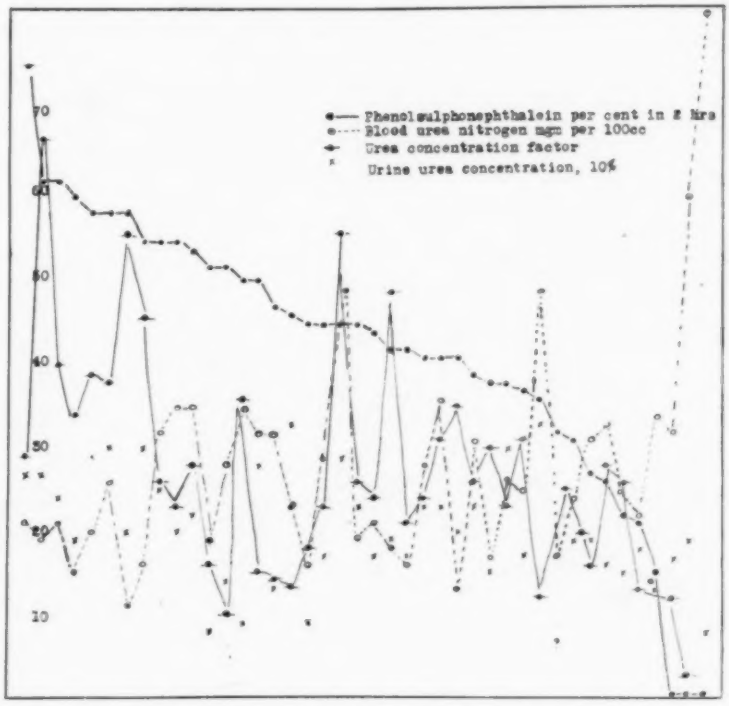

Chart 5.—Phenolsulphonephthalein excretion from normal to low.

to results inconsistent with the clinical picture. The comparative results of all the different tests used in these cases are recorded graphically. For detailed data of these cases the reader is referred to the original article.[4] In Chart 2 the blood urea concentration findings are recorded from normal to abnormal values consecutively. The same is done in Chart 3 with the urine urea concentration, in Chart 4 with the urea concentration factor and in Chart 5 with the phenolsulphonephthalein excretion. In each instance all other data obtained in the same case are recorded. It will be noted that the results of the urea concentration factor, approximate the blood and urine data, showing either improvement or a decrease in function. The phenolsulphonephthalein results show no such relation with either blood urea, urine urea concentration, or the urea concentration factor.

CONCLUSIONS

In renal lesions associated with azotemia or any other evidence of impairment in excretion of nitrogenous substance, the urea concentration factor appears to be a more sensitive test for renal efficiency than the other tests now in use. A distinct advantage of this test is that a combination of both blood and urine studies must be made in each case.

TREATMENT BY SPLENECTOMY OF ESSENTIAL THROMBOCYTOPENIA (PURPURA HEMORRHAGICA) *

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The rôle of the blood platelets in hemophilia and purpura hemorrhagica, which comprise the hemorrhagic diseases, is of paramount importance. Hemophilia is the result of some qualitative change in the blood platelets (Fonio,[1] Minot and Lee [2]) resulting in defective coagulation of the blood. Purpura hemorrhagica is accompanied by a qualitative change and by a greatly diminished number of blood platelets; also by some change in the capillary activity resulting in a hemorrhagic tendency. This constant diminution of the platelets without any known cause (Denys,[3] Hayem [4]) has given rise to the better modern name of essential thrombopenia (Frank [5]) or better still, thrombocytopenia (Eppinger [6]). Essential thrombocytopenia is a distinct clinical entity and is characterized by the following main features:

1. Diminution of the blood platelets. The average number of blood platelets in normal blood is 250,000. The platelets vary from none to 100,000 in this disease; at times the number may reach the normal figure. Hemorrhagic manifestations come into evidence when they fall below 60,000.

2. Preservation of normal coagulation time of the venous blood.

3. Prolongation of bleeding time (Duke [7]). Puncture of the lobe of the ear is followed by some oozing of blood for from one to three minutes normally. In thrombocytopenia this is prolonged usually from ten minutes to hours.

4. Positive capillary resistance test (Hess [8]). A tourniquet applied to the arm sufficient to prevent the return circulation without obliterating the pulse is followed by a shower of petechiae.

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*From the First Medical Division, Mount Sinai Hospital, New York.

1. Fonio: Cor.-Bl. f. Schweiz. Aerzte **45**:1505, 1915.
2. Minot, G. R., and Lee, R. I.: Blood Platelets in Hemophilia, Arch. Int. Med. **18**:474 (Oct.) 1916.
3. Denys, J.: La Cellule **3**:445, 1887.
4. Hayem, G.: Presse méd. **3**:233, 1895.
5. Frank, E.: Berl. klin. Wchnschr. **52**:454 and 490, 1915.
6. Eppinger, H.: Die hepatolienalen Erkrankungen in Enzyklopädie der Klinischen Medizin, 1920.
7. Duke, W. W.: The Pathogenesis of Purpura Hemorrhagica with Especial Reference to the Part Played by Blood Platelets, Arch. Int. Med. **10**:445 (Nov.) 1912.
8. Hess, A. F.: Hemophilia, Arch. Int. Med. **17**:203, (Feb.) 1916.

5. Failure of clot retraction (Hayem [9]). Clot retraction does not occur before splenectomy in this disease even when the blood platelets increase to 80,000. In a few obscure cases the blood platelets may be normal in number without clot retraction but accompanied by the other characteristics of essential thrombocytopenia, such as a prolonged bleeding time and positive capillary resistance test. Glanzmann [10] has attributed this to some defect of the blood platelets and has called this condition thrombasthenia.

The clinical manifestations of thrombocytopenia are:

1. Acute or chronic thrombocytopenia. A patient with an acute case may get well, run a short fatal course or his case may become chronic. The chronic condition as a rule appears in young persons, usually girls.

2. Apparently spontaneous hemorrhages into the skin and from mucous membranes, which may be continuous or intermittent.

3. Excessive hemorrhage from slight trauma. The outcome is usually weakness and physical incapacity, owing to a severe grade of anemia following the intermittent attacks of hemorrhage. Death not infrequently occurs from exsanguination.

PATHOGENESIS

Capillary hemorrhage is normally stopped by the production of a small blood platelet thrombus and by the inherent contractility of the vessels. The thrombus results from the adhesion and rapid agglutination of the blood platelets in the opening of the vessel from which the blood is oozing. The thrombus acts like a dam and prevents further bleeding.

One of the normal functions of the circulating blood platelets is to prevent the diapedeses of the red blood cells between the endothelial cells of the capillaries (Frank [11]). There is also some proof that the blood platelets participate in the control of vascular contractility (O'Connor,[12] Janeway [13]); this contractility also reenforces the protective mechanism against capillary hemorrhage. Any disturbance in the production or of the function of the blood platelets brings about a bleeding tendency due to the subsequent effect on the activity of the capillaries. The slightest trauma to the body then becomes evident by the appearance of hemorrhages, often uncontrollable. An examination of the blood during such a period in a case of essential thrombocytopenia will reveal the marked diminuion of the blood platelets, usually below

9. Hayem, G.: Compt. rend. Acad. d. sc. **123**:894, 1896.
10. Glansmann: Jahrb. f. Kinderheilk. **88**:1 and 113, 1918.
11. Frank, E.: Eulenburgs Real-Enzyklopädie, dritter Ergänzungsband Ergebnisse der gesamten Medizin, Berlin **3**:171, 1922.
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13. Janeway, T. C.; Richardson, H. B., and Park, E. A.: Experiments on the Vasoconstrictor Action of Blood Serum, Arch. Int. Med. **21**:565 (May) 1918.

100,000 and occasionally as low as 50. We have never observed their complete disappearance when they are counted directly in undiluted citrated plasma. In the intermittent type of thrombocytopenia the hemorrhagic tendency becomes evident when the number of blood platelets falls below 10,000, or less. Clot retraction is usually absent even when the blood platelets are as high as 80,000. There is a certain parallelism between the bleeding time, capillary resistance test and the number of blood platelets.

Concerning the cause of the thrombocytopenia there are two main theories: (1) Diminished production of the blood platelets as a result of some toxic or inhibitory action of the spleen on the megakaryocytes of the bone marrow which, according to Wright,[14] are the mother cells of the blood platelets. This theory proposed by Frank[5] led to the treatment of chronic thrombocytopenia by means of splenectomy. (2) In such cases Minot[15] found no diminution of the megakaryocytes in the bone marrow. Kaznelson frequently noticed enlargement of the spleen and came to the conclusion that an increased function on the part of this organ in the destruction of blood platelets was responsible for their diminution in the blood. Kaznelson[16] was the first to apply this knowledge and have a splenectomy performed in a case of chronic thrombocytopenia. The spleen of this case showed the presence of numerous large blood platelets. He suggested the name thrombolytic purpura for the condition. We shall discuss the validity of these theories later.

SPLENECTOMY FOR ESSENTIAL THROMBOCYTOPENIA

The exceptionally good results from splenectomy reported by Kaznelson[17] soon made the procedure the method of choice as a remedial or life saving measure in this disease when all other therapy has failed. So far seventeen cases of essential thrombocytopenia (including two reported in this paper) have been treated by splenectomy (Table 1).

The postoperative course in all the successful cases was about the same. The following points are noteworthy:

1. Blood platelet crisis. The increase varied from 25,000 to 1,500,000.

2. Immediate cessation of the hemorrhagic tendency. In a few cases the tendency reoccurred, but not as severely as formerly.

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14. Wright, J. H.: Boston M. & S. J. **154**:643, 1906.
15. Minot, G. R.: Diminished Blood Platelets and Marrow Insufficiency, Arch. Int. Med. **19**:1071 (June) 1917.
16. Kaznelson, P.: Wien. klin. Wchnschr. **29**:1451, 1916.
17. Kaznelson, P.: Ztschr. f. klin. Med. **87**:133, 1919.

3. Later return of the blood platelets to their previous low level. This took place from a few days to a few weeks after the splenectomy.

4. Increase of the hemoglobin and the red blood cells.

5. Apparent cure of the condition.

The remarkable results reported from splenectomy led us to undertake this procedure in two cases of essential thrombocytopenia in which all known methods of treatment, especially transfusion, had failed. Both patients were in a serious condition and were almost moribund. Splenectomy brought about immediate improvement and apparent ultimate cure and undoubtedly acted at the time of operation as a life-saving measure.

TABLE 1.—*Patients Treated by Splenectomy for Essential Thrombocytopenia*

Case	Date	Author	Result
1	1916	Kaznelson: Wien. klin. Wchnschr. **29**: 1451, 1916; Ztschr. f. klin. Med. **87**: 133, 1919	Well
2	1916	Kaznelson: Wien. klin. Wchnschr. **29**: 1451, 1916; Ztschr. f. klin. Med. **87**: 133, 1919	Well
3	1916	Kaznelson: Wien. klin. Wchnschr. **29**: 1451, 1916; Ztschr. f. klin. Med. **87**: 133, 1919	Greatly improved
4	1917	Benecke: Therapie der Gegenwart **19**: 418, 1917	Well
5	1917	Schmidt: Wien. klin. Wchnschr. **30**: 959, 1917	Well
6	1917	Schmidt: Wien. klin. Wchnschr. **30**: 959, 1917	Greatly improved
7	1919	Minkowski: Med. Klin. **15**: 1243, 1919	Greatly improved
8	1920	Ehrenberg: Monatschr. f. Geburtsh. u. Gynäk. **51**: 99, 1920	Well
9	1921	Eylenburg: Folia Hemat. **26**: 176, 1921	Well
10	1921	Kaznelson: Med. Klin. **17**: 974, 1921	Died
11	1921	Kaznelson: Med. Klin. **17**: 974, 1921	Well
12	1921	Minot: Med Klin. **17**: 974, 1921	Well
13	1922	Cori: Ztschr. f. klin. Med. **94**: 350, 1922	Well
14	1922	Steinbrinck: Ztschr. f. klin. Med. **94**: 447, 1922	Greatly improved
15	1923	Bowen: Bull. Buffalo Gen. Hosp. **1**: 2, 1923	Well

REPORT OF CASES

CASE 1.—*R. G., chronic essential thrombocytopenia (purpura hemorrhagica); splenectomy; recovery.*

History.—A girl, aged 19, was admitted to the first medical service, Mount Sinai Hospital, on Oct. 26, 1922, complaining of uncontrollable bleeding from the nose, mouth and stomach. The family history and past history were negative. There were no bleeders in the family. The patient was perfectly well until she was 5 years of age, when she had an attack of "kidney trouble" (bloody urine and generalized edema). This was followed a few weeks later by an uncontrollable nasal hemorrhage, for which the child had to be taken to a hospital, where she remained for five weeks. Since then, about once each year, the patient had had an attack of severe bleeding from the nose and mouth and vomiting of blood. During the attacks she became weak and pale. The bleeding continued at varying intervals from one to five days, occasionally for a longer period. In the interval between attacks the patient usually felt quite well. However, she always noticed black and blue spots on her skin; these occurred after the slightest trauma. The menses during an attack were usually repressed. Recently the periods had been greatly prolonged.

The present attack began three days before admission after the patient had apparently been well for two years. There had been bleeding at intervals from the nose and mouth. Some of the blood coming down from the back of the nose was swallowed and then vomited.

Eight transfusions had been given within the past eight years without producing any lasting effect.

Physical Examination.—The patient was fairly well nourished, well developed and acutely ill. There was marked pallor of the face. She vomited dark red blood repeatedly. She had pyorrhea. The gums were somewhat spongy but they were not bleeding. Blood clots were seen in the pharynx. She had bilateral adenopathy. There was a loud blowing systolic murmur at the apex of the heart not transmitted. The liver was not palpable. The spleen was felt 1 cm. below the costal margin. There was slight pretibial edema. There were old scars and pigmented areas. There were widely distributed hemorrhagic areas varying in size from a petechia to a large ecchymosis. These areas were most marked on the legs and were confluent.

Treatment and Course.—On Oct. 26, 1922, direct transfusion (Unger method) of 600 c.c. was performed. There was no bleeding for five days following this transfusion. A distinct increase in the size of the spleen was noted, 3 cm. below the costal margin. Oct. 30, 1922, blood examination revealed: hemoglobin, 38 per cent. (Kuttner); red cells, 2,272,000; white cells, 6,800; platelets, 6,400; differential count, 300 cells counted: polymorphonuclear neutrophils, 54.3 per cent.; polymorphonuclear eosinophils, 1.6 per cent.; polymorphonuclear basophils, 2 per cent.; myelocytes, neutrophilic, 1.3 per cent.; lymphocytes, 25.6 per cent.; plasma cells, 2 per cent.; monocytes, 13 per cent.; and normoblasts, 1 per 300 white cells. The coagulation time of the blood was ten minutes (test tube). Bleeding was profuse at the end of ten minutes. The capillary resistance test was positive within two minutes. There was no clot retraction.

Diagnosis: Secondary anemia, essential thrombocytopenia.

Nov. 2 to Nov. 5, 1922: There was repeated vomiting of old and fresh blood. On examination of the throat, bright red blood was seen issuing from the nasopharynx.

Nov. 5, 1922: The hemoglobin content was 27 per cent. Direct transfusion (Unger method), 500 c.c., was performed.

Nov. 9, 1922: Slight epistaxis. The patient vomited blood once.

Nov. 13, to Nov. 15, 1922: Slight epistaxis and vomiting blood. On November 15, 20 c.c. of horse serum was given intramuscularly without effect.

Nov. 16, 1922: The hemoglobin content was 32 per cent. Direct transfusion (Unger method), 750 c.c., was performed. There was no reaction.

Nov. 19, 1922: The hemoglobin content was 43 per cent. Vomiting blood again occurred.

Nov. 20 to Nov. 25, 1922: During this period the patient vomited blood repeatedly. During the later hemorrhages the pulse was so rapid that it was almost impossible to count. Otherwise the pulse varied from 120 to 140. There was marked pallor. The eyes were large and starey at times. The patient was very restless.

Nov. 26, 1922: Direct transfusion (Unger method), 500 c.c., was performed.

Nov. 27, 1922: The hemoglobin content was 35 per cent. The general condition was poor, the pallor still marked, expression anxious. There was slight epistaxis. The patient vomited once. Most of the veins of the forearms were tender and cordlike, evidently due to intravascular clotting, making the transfusions difficult.

It was decided that splenectomy would be tried after the next transfusion, which was to be given to improve the patient's general condition.

Dec. 1, 1922: Direct transfusion (Unger method), 500 c.c., was performed. The transfusion had to be stopped at this point because the patient complained of severe precordial pain.

Dec. 2, 1922: The hemoglobin content was 43 per cent. A splenectomy was performed by Dr. A. A. Berg. A greatly enlarged spleen was delivered through a subcostal incision. The wound bled considerably. As soon as the pedicle was clamped all bleeding stopped. There was some oozing from the nose throughout the anesthesia; this also stopped as soon as the spleen was removed. A direct transfusion of 800 c.c. was given immediately after the operation. The postoperative recovery was uneventful. The wound healed by primary union.

Summary of report by Dr. F. S. Mandlebaum: The macroscopic specimen consisted of a large spleen weighing 1,400 gm. and measuring 23 by 13 by 6.5 cm. The surface was smooth with occasional indentation. There were few adhesions on the mesial aspect. The vessels were patent and not sclerotic. The spleen felt elastic and cut easily. The cut surface showed the presence of numerous large follicles. Pulp was present in a normal amount. The sinuses were not dilated or sclerosed. Microscopically the spleen showed myeloid metaplasia and hyperthrophy of the malpighian bodies. There were no blood platelets or thrombi.

On Dec. 2, 1922, six hours after the operation, crops of fresh petechiae appeared over the upper part of the left side of the chest and left cheek. All

TABLE 2.—*R. G., Case 1, Blood Examinations Following Splenectomy, Dec. 2, 1922*

	Hemoglobin, Percentage	Red Blood Cells	White Blood Cells	Platelets	Polymorphonuclears, Percentage	Lymphocytes, Percentage	Monocytes, Percentage	Coagulation Time, Min.	Bleeding Time, Min.	Capillary Resistance Test	Clot Retraction
After 6 hours*	70	4,352,000	56,000	96,000	97.0	0.3	2.3	..	..	.....	.....
12/ 3/22	66	4,144,000	40,000	225,000	93.3	2.0	4.6	..	1½	.....	.....
12/ 4/22	68	4,064,000	39,200	296,000	87.6	3.0	9.3	..	2	.....	.....
12/ 5/22	60	3,872,000	16,000	220,000	73.6	13.0	12.6	..	1	.....	.....
12/ 6/22	62	3,962,000	14,400	270,000	86.0	8.6	5.3	..	2	.....	.....
12/ 8/22	63	3,880,000	15,800	145,000	85.0	8.6	5.0	..	1½	.....	.....
12/ 9/22	66	4,160,000	15,000	240,000	74.0	13.6	8.6	..	2	Negative	.....
12/11/22	75	4,544,000	7,000	60,000	63.0	18.3	15.3	..	4	.....	.....
12/12/22	75	4,480,000	7,000	25,000	46.6	31.0	17.0	..	3	.....	.....
12/13/22	72	4,520,000	6,800	5,000	60.0	24.0	13.3	..	8	.....	.....
12/15/22	71	4,488,000	8,900	30,000	50.6	24.3	20.3	..	2	Negative	.....
12/16/22	70	4,960,000	10,000	3,000	66.6	14.0	18.3	..	5	.....	.....
12/17/22	72	5,120,000	9,600	5,000	44.3	32.2	12.0	..	4	.....	.....
12/19/22	77	4,832,000	10,600	4,800	65.3	17.6	12.0	10	3	Negative	Very slight
12/22/22	68	4,480,000	9,000	6,000	62.3	26.6	7.3	..	2	.....	.....
12/24/22	76	4,736,000	12,200	3,000	56.6	28.0	12.0	..	2	.....	.....
12/26/22	74	4,800,000	10,200	4,000	61.0	28.3	9.0	..	2	.....	.....
12/28/22	82	5,200,000	12,400	7,500	53.3	32.0	12.3	..	1½	.....	.....
1/ 1/23	74	4,576,000	10,200	10,000	59.0	30.3	9.6	..	2	.....	.....
1/ 5/23	71	4,512,000	7,800	5,000	31.6	47.0	10.6	..	½	.....	.....
1/ 9/23	70	4,120,000	12,000	4,000	45.3	32.6	17.6	..	9	Negative	.....
1/13/23	80	5,120,000	11,600	10,000	48.6	42.3	6.3	..	½	.....	.....
1/17/23	80	5,632,000	16,000	6,000	54.0	36.6	9.0	..	..	.....	.....
1/24/23	76	4,736,000	12,800	8,000	57.3	33.3	7.6	..	0	.....	.....
1/27/23	87	5,376,000	13,800	10,000	52.6	36.6	10.3	11	3	Negative	None
1/31/23	87	5,440,000	28,000	14,000	51.0	39.0	19.3	..	..	.....	.....
2/ 3/23	80	5,564,000	19,800	16,000	53.3	36.6	9.0	..	..	.....	.....
2/10/23	90	5,864,000	11,200	12,000	54.0	28.0	6.3	..	..	.....	.....
2/13/23	92	6,194,000	12,400	12,000	57.0	36.6	5.3	8	3	Slightly positive	Present
4/24/23	84	6,656,000	14,200	20,000	62.6	26.3	9.6	6	4½	Negative	Present

* Following two transfusions.

bleeding from the mucous membranes stopped. The hemoglobin content rose to 70 per cent.

Dec. 2, 1922, to April 10, 1923: There was steady improvement. The color gradually returned; the cheeks and lips were red. The patient felt perfectly well. There was a cessation of all hemorrhage from the nose. For a short period after the splenectomy there was slight bleeding from the gums but none after that. The patient vomited three times after the operation, but there was no blood in the vomitus. She vomited a slight amount of blood only once later. Petechiae appeared about six hours after the operation, but none had appeared since. All the hemorrhagic areas disappeared. Black and blue marks did not appear as formerly. Recently the patient "turned" her knee cap, but only a slight skin hemorrhage developed. Before operation there was a marked urobilin reaction in the urine; after operation, a faint trace.

Blood Changes Following Splenectomy (Chart 1; Table 2): (*a*) The two transfusions—500 c.c. given the day before the operation and 800 c.c. given immediately after the operation—raised the hemoglobin to 70 per cent. and the red cells to 4,352,000. The following month the hemoglobin fluctuated between 60 and 80 and then rose to 90 per cent. The red cells also followed the high percentage and later rose to 5,864,000. Four months later the hemoglobin again fell to 80 per cent., but the red cells remained over five and one-half million.

(*b*) The leukocytes increased to 56,000 but gradually assumed their normal number (5,600 to 7,000), and later fluctuated between 8,000 to 28,000. After the postoperative polynucleosis there followed a persistent monocytosis.

(*c*) The blood platelets showed the usual behavior as in other splenectomized cases of thrombocytopenia. Six hours after the operation 95,000 platelets were present. The following day they rose to 225,000 and again rose on the second

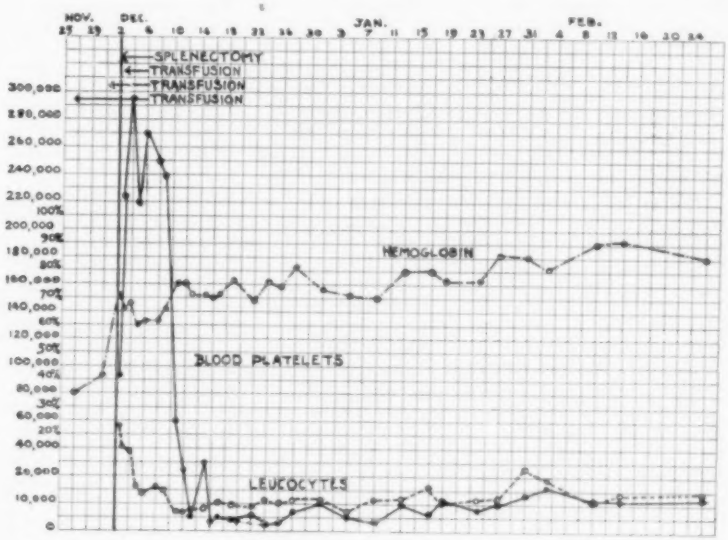

Chart 1 (Case 1).—Variations of the hemoglobin, leukocytes and blood platelets following splenectomy.

day after operation to 295,000. Then within a week the platelets dropped to 5,000. After this the bleeding time was usually normal. Occasionally it was prolonged. The blood platelets were distinctly larger than normal ones.

(*d*) The capillary resistance test was usually negative. On one occasion a few petechiae appeared at the bend of the elbow.

(*e*) Slight clot retraction was present the first month. During the second month there was no clot retraction. Clot retraction appeared again the third month, but this was somewhat less than normal. Clot retraction was present at a recent examination (April 24, 1923).

Summary of Case.—The patient had an essential thrombocytopenia (purpura hemorrhagica) of fourteen years' duration with chronic intermittent course. The patient became exsanguinated several times and received transfusions as many times, with only temporary success. All agents known to stop hemorrhage

were of no avail until splenectomy was performed, following which there was no further bleeding. The patient was discharged apparently well. The hemorrhagic tendency had stopped.

CASE 2.—Chronic essential thrombocytopenia (purpura hemorrhagica); splenectomy; recovery.

History.—A boy, aged 15, was admitted to the first medical service on Nov. 22, 1922, complaining of bleeding from the nose and vomiting of blood. The family history and past history were negative. There were no bleeders in the family. The present illness began in April, 1919, when the patient had an attack of tonsillitis followed by hemorrhages into the skin, bleeding from the gums, painful joints, vomiting and pain in the upper part of the abdomen. He also had irritability of the eyes, weakness, fever, chills and sweats. He remained in the hospital for one month. He was apparently well except for an occasional ecchymosis following some slight trauma, until May, 1922, when he received a blow on the nose. This was followed by a severe epistaxis which continued for several hours. The bleeding was stopped by means of a tampon saturated with fresh normal blood. The skin hemorrhages had become more frequent since. In July, 1922, while drinking milk, blood began to issue from the anterior and posterior nares, and soon the patient vomited blood and food. Some hemorrhagic areas again appeared on the skin and roentgen-ray therapy was applied to the splenic region, with apparently good results. His condition improved. He lived a quiet life until the day of his recent admission to the hospital, Nov. 22, 1922, when he was again struck on the nose, and he had been bleeding and vomiting blood ever since.

Physical Examination.—The patient was a well developed and fairly well nourished boy with marked pallor. He appeared to be acutely ill. There were a few petechiae in the conjunctivae of both lower lids. The teeth were in fair condition. The gums were spongy and bleeding, the tonsils large and covered with hemorrhagic spots. The heart was not enlarged. There was a systolic thrill and murmur at the apex. The spleen was not palpable, but it was large to percussion. There were numerous petechiae over the back, chest, abdomen, thighs and legs.

On Nov. 26, 1922, the blood count was: hemoglobin, 45 per cent.; red cells, 2,584,000; white cells, 10,000; platelets, 10,000 (plasma); polymorphonuclear neutrophils, 71.6 per cent.; polymophonuclear eosinophils, 1.6 per cent.; polymorphonuclear basophils, 0.3 per cent.; lymphocytes, 15.3 per cent.; and monocytes, 11 per cent. The coagulation time of the blood was ten minutes; the bleeding time four and one-half minutes.

The tourniquet test was slightly positive. There was no clot retraction. The patient had secondary anemia, thrombocytopenia and monocytosis. The blood picture was characteristic of essential thrombocytopenia.

Treatment and Course.—Nov. 29, 1922: There were no further hemorrhages. The petechiae on the legs had disappeared. The spleen was not palpable.

Dec. 2, 1922: The patient had epistaxis at intervals all day.

Dec. 6, 1922: The hemoglobin content gradually fell until it was 28 per cent. The patient still bled daily from the nares. The platelets numbered 8,000.

Dec. 9, 1922: The gums were spongy and bleeding. The condition was becoming worse. The bleeding from the nose had stopped.

Dec. 12, 1922: Slight bleeding from the gums continued. There was marked pallor and weakness. Blood examination (Table 4) showed: hemoglobin, 28 per cent.; red cells, 2,204,000; and platelets, 400. The bleeding and coagulation time were normal. The capillary resistance test was negative, but there was no clot retraction.

Dec. 16, 1922: The patient vomited about 7 ounces of dark clotted blood. The blood trickled down from the posterior nares.

Dec. 17, 1922 at 12:50 a. m.: There was bleeding both from the anterior and posterior nares. Thromboplastin and epinephrin did not control bleeding. The tampon was not tolerated. Twenty cubic centimeters of unmodified blood

injected intramuscularly and 10 c.c. injected slowly into the nose arrested the bleeding. The hemoglobin content was 30 per cent. Early in the morning 4 a. m.) the patient again began to bleed from the nose. The pulse was rapid, 140; later (6:30 a. m.), 150. The hemoglobin content was 29 per cent.; platelets, 300 (plasma). Direct transfusion (Unger method), 500 c.c., was performed.

Dec. 18, 1922: There had been no bleeding since the transfusion was performed. There was a slight rise in temperature to 102.8 F. The hemoglobin content was 38 per cent.; red cells, 2,634,000; white cells, 19,400; polymorphonuclear neutrophils, 91 per cent.; lymphocytes, 7 per cent.; monocytes, 2 per cent.; and platelets, 27,500. The bleeding time was thirteen minutes the coagulation time, eight minutes. The capillary resistance test was negative. There was no clot retraction.

Dec. 19, 1922: There was a crop of new petechiae on all extremities.

Dec. 22, 1922: The patient had edema of the uvula and tonsil—traumatic.

Dec. 23, 1922: The hemoglobin content was 28 per cent.; red cells, 2,010,000; platelets, 24,000.

Dec. 25 to Dec. 29, 1922: Fresh petechiae appeared daily. The general condition was becoming worse. Pallor and weakness were marked.

Dec. 29, 1922: Splenectomy was decided on for the relief of the condition.

TABLE 3.—*Case 2, Blood Examinations Before Splenectomy*

	May 5, 1919	May 1, 1922	Nov. 26, 1922	Dec. 18, 1922	Dec. 30, 1922
Hemoglobin	70%	78%	45%	38%	48%*
Red cells	3,960,000	4,800,000	2,584,000	2,634,000	2,896,000
White cells	23,000	14,300	10,000	19,400	22,000
Platelets	80,000	80,000	10,000	24,000	None
Polymorphonuclear neutrophils	83%	63.5%	71.6%	91%	72.3%
Lymphocytes	13%	27.5%	15.3%	7%	14.3%
Monocytes	4%	7.5%	11.0%	2%	6.3%
Coagulation time	5 min.	13 min.	10 min.	8 min.	4 min.
Bleeding time	7 min.	16 min.	4½ min.	13 min.	Profuse at end of 6 min.
Capillary resistance test	Slightly positive	Slightly positive	Slightly positive	Positive	Slightly positive
Clot retraction	None	None	None	None	None

* Day following transfusion of 500 c.c. whole blood.

Direct transfusion (Unger method), 450 c.c., was performed. There was a severe reaction following transfusion. The patient had a chill with rise of temperature to 105 F.

Dec. 30, 1922: Splenectomy was performed by Dr. E. Beer through a subcostal incision. There was profuse oozing of the wound. Continuous oozing from the nose occurred during the anesthesia.

A soft, slightly enlarged spleen with omental adhesions between the stomach and hilus was found. The adhesions were doubly divided and cut. The spleen was delivered with some difficulty. The hilus was ligated and cut, taking special care not to include the adherent stomach.

Summary of Pathologic Report by Dr. F. S. Mandlebaum: The macroscopic specimen consisted of a moderately enlarged spleen weighing 300 gm. and measureing 14 by 7.5 by 3 cm. It was elastic and cut easily. Malpighian bodies were visible. Microscopic examination showed only hyperthrophy. No blood platelets were found.

Immediately after the removal of the spleen, all oozing of blood stopped from the wound and nose. The same effect was noted for the bleeding time as in the previous case.

The bleeding before splenectomy was profuse at the end of six minutes, when it was stopped. The bleeding time during manipulation at the hilus was six minutes; immediately after splenectomy, three minutes; two hours after splenectomy, three minutes; eight hours after splenectomy, three minutes; and fifteen hours after splenectomy, two and one-half minutes (Tables 3 and 4).

Dec. 31, 1922: The blood pressure was: systolic 95; diastolic 70. The pulse rate was 160; later, 132. Digifolin, 15 minims, was administered every three hours. Rectal drip was given for two hours alternated with two hours when it was not given.

Jan. 1, 1923: The general condition was much improved. There was slight abdominal pain, especially in the wound, and also slight precordial pain. There was no bleeding.

Jan. 2, 1923: There was slight nose bleed once during the night.

Jan. 3, 1923: There was nose bleed once during the day.

Jan. 4, 1923: There was slight bleeding again from the nose; a few drops of blood oozed out and stopped immediately, never oppressive nor profuse as on previous occasions.

Jan. 7, 1923: There was a slight serosanguinous discharge from the wound.

Jan. 8, 1923: The sutures were removed, accompanied by bleeding easily controlled with epinephrin.

TABLE 4.—*Case 2, Blood Examinations After Splenectomy*

	Hemoglobin, Percentage	Red Blood Cells	White Blood Cells	Platelets	Polymorphonuclears, Percentage	Lymphocytes, Percentage	Monocytes, Percentage	Coagulation Time, Min.	Bleeding Time, Min.	Capillary Resistance Test	Clot Retraction
After 2 hours*	64	3,232,000	36,000	81,200	90.6	2.6	3.3	..	3	.....	.....
12/31/22	51	2,888,000	55,000	12,000	94.0	1.3	4.3	..	..	.....	.....
1/ 1/23	45	2,992,000	30,400	10,000	90.0	3.0	7.0	..	5	.....	.....
1/ 2/23	40	2,896,000	19,400	1,000	89.0	4.0	6.6	..	10	.....	.....
1/ 3/23	38	2,832,000	14,000	2,000	82.0	7.3	9.0	..	10	.....	.....
1/ 4/23	40	2,656,000	14,400	4,800	80.3	7.0	10.3	..	5	.....	.....
1/ 5/23	47	2,884,000	27,000	8,000	74.3	10.3	13.3	10	4	Slightly positive	None
1/ 6/23	46	2,936,000	14,000	4,000	75.3	14.0	7.0	..	8	.....	.....
1/ 8/23	49	3,450,000	12,000	4,000	72.0	15.6	8.3	..	10	.....	.....
1/10/23	60	3,992,000	13,200	10,000	73.6	14.3	9.6	7	8	Slightly positive	None
1/13/23	56	3,520,000	14,400	4,000	75.3	15.3	6.3	..	..	.....	.....
1/19/23	60	4,800,000	21,000	14,000	72.0	18.0	8.0	..	10	Slightly positive	.....
1/27/23	58	4,536,000	14,400	14,000	59.3	27.0	11.0	11	8	Slightly positive	None
1/31/23	59	4,480,000	12,000	10,000	53.3	40.3	6.3	..	..	.....	.....
2/ 3/23	76	4,808,000	18,000	6,000	57.3	28.6	11.0	..	4	.....	.....
2/ 7/23	76	4,816,000	14,600	8,000	57.0	32.3	8.0	12	3	Slightly positive	None
2/14/23	80	4,704,000	15,000	12,000	56.6	34.6	4.3	6	3	Slightly positive	Present but slight
3/23/23	80	4,736,000	18,200	14,000	49.6	44.6	4.3	8	3	Negative	Present
4/ 6/23	81	4,840,000	10,400	20,000	48.0	42.3	9.0	12	2	Negative	Present
5/26/23	83	5,120,000	9,000	50,000	44.3	41.3	10.6	9	2	Negative	Present

* Done after a blood transfusion.

Jan. 11, 1923: All sutures were out. There was slight bleeding from the wound not controlled by thromboplastin. Epinephrin controlled the bleeding more satisfactorily. There was slight nose bleed which was stopped with epinephrin.

Jan. 19, 1923: The patient was out of bed. Many petechiae appeared on the legs and a few on the right lower conjunctivae.

Feb. 3, 1923: A few petechiae on the face and lower legs appeared from time to time. The gums had improved; there was no sponginess and no bleeding.

Feb. 8, 1923: There were hypostatic petechiae on the legs only. The general condition was excellent. The hemoglobin content was 76 per cent.

Feb. 14, 1923: For the first time clot retraction was present. There was a thrombocytopenia and slightly positive capillary resistance test. The petechiae were disappearing from the legs. There had been no hemorrhages since Feb. 9, 1923.

Feb. 17, 1923: The patient was discharged well.

Blood Changes Following Splenectomy (Chart 2; Table 4): (1) Hemoglobin and Red Blood Cells: The transfusion of 500 c.c. before splenectomy raised the hemoglobin to 48 per cent. and the transfusion given immediately after the operation produced a further rise to 60 per cent. and a rise to 3,232,000 red blood cells. This gradually dropped during the first four days to 38 per cent. hemoglobin and 2,832,000 red blood cells. Improvement then began and at the last examination (April 6, 1923) the hemoglobin was 81 per cent. and the red blood cells were 4,840,000. Normoblasts and Howell-Jolly red cells were occasionally present.

(2) White Blood Cells: Just before the operation there was a leukocytosis of 22,000; six hours after the operation the leukocytes were 36,000, and on the following day they rose to 55,000. The differential blood picture after the

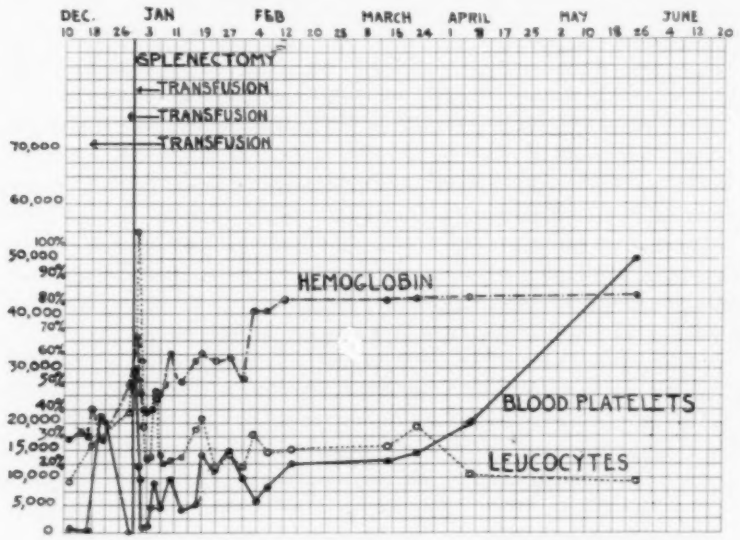

Chart 2 (Case 2).—Variations of the hemoglobin, leukocytes and blood platelets following splenectomy.

postoperative polynucleosis showed a persistent monocytosis (increase of the large mononuclears and transitionals).

(3) Blood Platelets: The day following the operation there was a slight rise to 31,200; then a gradual fall to 1,000 on the third day after the operation. After this there was a gradul increase to 10,000, and then to about 20,000. The morphology remained about the same. The day following the operation a few giant blood platelets appeared in the smears.

(4) Bleeding Time: For a month and a half this was prolonged, usually over two minutes, and even as long as twelve minutes. This became normal (two to three minutes).

(5) Tourniquet Test (Capillary Resistance): This was constantly positive until the third month after the operation. It then became constantly negative.

(6) Clot Retraction: There was no clot retraction for six weeks after the operation. This appeared on Feb. 14, 1923, and slight clot retraction remained

present although the blood platelets remained low. It is interesting to note that the blood of this patient never showed clot retraction on previous examinations.

Summary.—This was a case of chronic thrombocytopenia of four years' duration. The patient's condition became worse as time went on; the bleeding was more frequent and more severe. Splenectomy brought about a turn for the better, and the patient has steadily improved since.

The patient was again seen in April, 1923. He had had no hemorrhages since he left the hospital. He had gained weight and strength steadily. Static purpura of the legs did not occur. The examination of the blood still showed a thrombocytopenia (blood platelets, 22,000), but all other evidence of the previous condition was absent. The capillary resistance test was negative and clot retraction was present.

DISCUSSION

A study of the blood changes following splenectomy in our cases brings us a step nearer to the solution of the underlying factors in the production of the thrombocytopenic syndrome. This tends to show that, first, the inhibitory action of the spleen on the megakaryocytes of the bone marrow suggested by Frank,[6] or, second, the thrombolytic or blood platelet destructive action of the spleen as suggested by Kaznelson [17] are not explanatory theories of the pathogenesis of this disease. The first case described by Kaznelson probably belongs to a different subgroup of the thrombocytopenic purpuras, because he found large numbers of blood platelets in the sinuses of the spleen. Examination of our spleens showed neither in smears nor in cut sections any abnormal increase of the blood platelets; but, on the contrary, a marked diminution of the blood platelets was present. While the spleen apparently assumes a thrombolytic function normally, there is little evidence outside of Kaznelson's and a few other observations to show that in this type of purpura this supposed action of the spleen is increased.

It is remarkable in all these cases that with the removal of the spleen active hemorrhage immediately stops. This sudden cessation of hemorrhage would indicate that the function of the spleen in these cases could not be taken up so quickly by any vicarious action of other members of the hematopoietic or reticulo-endothelial system. It might indicate that when the spleen was removed some agency became active in inducing the capillaries to contract so as to stop all bleeding. Therefore it tends to show that the normal spleen has some controlling mechanism on capillary activity through the medium of the blood platelets.

From our observation it would appear that the spleen does not function in inhibiting the activities of the megakaryocytes in the production of platelets, even though the removal of the spleen is followed by their temporary increase in the circulating blood, because the blood platelets quickly return to their diminished number or even to a lower level. It would appear, however, that the spleen in these cases does

exert an influence on two important properties of the blood platelets, namely, the one which produces clot retraction and the property of the blood platelets to agglutinate to form thrombi. These properties may be restored immediately after the removal of the spleen or by a later steady development.

We believe that the main process is not entirely an inhibitory or a destructive one on the part of the spleen in this disease, but some damaging and to a certain extent a destructive mechanism exerted by the reticulo-endothelial system on the blood platelets. The damaging mechanism possibly resides in the reticulo-endothelial system, mainly in the spleen, hemolymph nodes, liver, lymph nodes and bone marrow. Splenectomy, while it does not influence the number of blood platelets in the circulation, induces a cessation of capillary hemorrhage. The influence of the reticulo-endothelial system in modifying the quality of the platelets varies in intensity from time to time, but it is always present. When an increase in function occurs it gives rise to the severer types of this disease, or when diminished, a milder action is manifest, as indicated when hemorrhage follows ordinary trauma.

Blood platelets have certain important vital properties: First, they furnish cytozyme (Bordet [18]) for the formation of the blood clot. Any alteration of this property leads to the condition of hemophilia in which the coagulation of the blood is markedly prolonged on account of the delay in the proper formation of cytozyme—the initial step in the coagulation of the blood. In essential thrombocytopenia cytozyme is rapidly formed, but the amount is necessarily diminished on account of the fewer platelets, and the clear citrated purpuric plasma does not clot after standing several hours, on account of the sedimentation of the platelets.

Second, the blood platelets have an agglutinative property (Bizzozero [19]) by virtue of which they rapidly adhere to cut or injured surfaces of the tissues, resulting in the formation of a thrombus. The minimum number of blood platelets necessary for this action on cut skin capillaries is low compared to what occurs in the essential thrombocytopenic state (Table 3). In pernicious anemia, leukemia and in a few cases of secondary anemia, we have found platelet counts below 10,000 without any prolongation of the bleeding time. In some cases of essential thrombopenia the bleeding time is prolonged, although the blood platelets may be as high as 250,000. In the rare condition of thrombasthenia the bleeding time is greatly prolonged, although the

18. Bordet, J.: Bull. Johns Hopkins Hosp. **32**:213, 1921.
19. Bizzozero: Virchows Arch. f. path. Anat. **90**:261, 1882.

blood platelets are always over 100,000. Third, clot retraction is also an important indicator of the condition of the platelets. Clot retraction may appear with less than 20,000 blood platelets. In essential thrombocytopenia this phenomenon is usually absent, although the platelets may be over 50,000, and in thrombasthenia it is absent with even a greater number of platelets.

This peculiar damaging action on the blood platelets by some element in the spleen and other organs does not account for the diminished number of blood platelets in the circulating blood. Following the initial rise after splenectomy they fall to their low figures, so that we must assume that there is some fault in their formation. The megakaryocytes are not diminished in number in the bone marrow in essential thrombocytopenia, but the fragmentation of the pseudopodia of these large cells does not take place properly, because the blood platelets in this disease are very large and irregular. Normally, a certain number of blood platelets are destroyed daily in the spleen. The results of such a destructive action in a case with defective blood platelet formation possibly leads to a further diminution of their number and to an altered function of these bodies

In some of the patients with thrombocytopenia who were operated on, the hemorrhagic tendency returned, but it was not as severe as formerly. Here we must assume that the remaining reticulo-endothelial system has taken up the function of the spleen and has exerted its dangerous influence on the few blood platelets formed. To combat this we must turn our attention to some methods of inhibiting the activity of this system. At present we are using roentgen-ray therapy and also foreign protein injections (milk, Gram [20]) with encouraging results in some unoperated cases. Their use in splenectomized cases may prove beneficial if there should be a recurrence.

The removal of the spleen is followed by a gradual return of the agglutinative and retractive properties of the blood platelets, although its removal has no effect on their formation. On the integrity of the blood platelets depends also the proper tonus and contractility of the capillaries. We need not go into the question of the relation of vascular constriction to the quality of the blood platelets. O'Connor,[12] Janeway [13] Hirose [21] and others have shown this intimate relation. It is noteworthy that the capillary resistance test in our cases was positive for a long time and was slightly positive occasionally in Case 1 until April 24, 1923. It is now persistently negative in this case.

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20. Gram, H. C.: Ztschr. f. klin. Med. **95**:51, 1922.

21. Hirose, K.: Relation Between the Platelet Count of Human Blood and Its Vasoconstrictor Action After Clotting, Arch. Int. Med. **21**:605 (May) 1918.

CONCLUSIONS

1. Splenectomy has a definite curative influence on the hemorrhagic factor of chronic thrombocytopenia.

2. It does not seem to be a determining factor in restoring the normal number of blood platelets to the circulating blood.

3. The disease seems to be associated with a disturbed function of the capillary wall in addition to a disordered state of the blood platelets, or it is a result of the diminution of the latter. This is evidenced by the occurrences of purpuric hemorrhages in the skin of the legs on prolonged standing and by the presence of a positive capillary resistance test. With the removal of the spleen the capillary resistance test disappears, as does the static purpura.

4. After splenectomy the quality of the blood platelets is restored, as is demonstrated by the reappearance of clot retraction and diminution of the bleeding time to normal.

BLOOD COUNTS IN HODGKIN'S DISEASE

REPORT OF CASES *

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NEW YORK

In 1911 and 1914, C. H. Bunting [1] published his papers on the blood count in Hodgkin's disease. He believed that the blood count was of real value from a diagnostic point and showed: (1) an increase in blood platelets, and (2) an absolute increase in the transitional leukocytes. Although no one appears to have attempted to disprove directly the work of Bunting, of late there seems to be a good deal of doubt as to the accuracy of his conclusions. Among those who doubt the diagnostic value of the blood count are Janeway [2] and Pepper.[3]

During the last four years, I have studied all of the cases of Hodgkin's disease in the Presbyterian Hospital wards and outpatient department. There have been eighteen cases that were diagnosed as Hodgkin's disease. Only those cases that were diagnosed by microscopic section were used in the series.

Blood counts were all made by myself; as a rule, 500 cells were counted. The only exceptions were Cases 7, 15 and 16. In these cases, 300 cells were counted. Both Hasting's and Wilson's stains were used and were equally satisfactory. Large mononuclears and transitionals (as described by Bunting [1]) were classified together, as it is frequently difficult to make a satisfactory distinction between them. The number of transitionals in normal blood varies considerably (from 2 to 4, Wood [4]; from 3 to 5, Webster [5]; from 6 to 8, Naegeli [6]; from 3 to

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1. Bunting, C. H.: Blood Platelets and Megalokaryocytes in Hodgkin's Disease, Bull. Johns Hopkins Hosp. **22**:114, 1911. The Blood Picture in Hodgkin's Disease, Ibid., p. 369. Hodgkin's Disease, Ibid. **25**:173, 1914.

2. Janeway, T. C.: A Case of Hodgkin's Disease with Skin Eruption, Med. Clin. North America, July, 1917, p. 20.

3. Pepper, O. H. Perry: Hodgkin's Disease with Jaundice as an Early Symptom, Med. Clin. North America, March, 1920, p. 1449.

4. Wood, T. C.: Chemical and Microscopical Diagnosis, New York, D. Appleton and Company, 1917, p. 103.

5. Webster, Ralph W.: Diagnostic Methods, Philadelphia, P. Blakiston's Sons and Company, 1920, p. 560.

6. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Leipzig, Von Veit, 1912, p. 186.

10, Gulland and Goodall [7]). Hence it is obvious that a transitional count must be at least 5 to be regarded as high.

The table shows that among the eleven untreated patients there were only two that had transitional counts of more than 5 per cent. Of the eight patients that had received treatment, there were four with transitionals higher than 5 per cent. and two with just 5 per cent. Hence, eight out of eighteen cases showed an increase in transitionals; two of these were only a little higher than normal.

TOTAL COUNTS

When the cases are arranged in order of total white cell count, there is no apparent relationship to the length of the disease. The highest white count was 13,000. The highest percentage of neutrophils are found in the higher counts.

PLATELETS

In Bunting's first paper, he mentions [1] platelet counts, all of which were high. He then compares these smears with other smears from cases of Hodgkin's disease and is convinced that the platelets are high, and in his later articles [1] he estimates the number of platelets by examining the smear. A skilled observer may well be able to obtain satisfactory results from an examination alone, but I have found it much more accurate to count the platelets, as one may occasionally be deceived by the thickness of the smear or by a tendency of the platelets to gather in groups, which is misleading. In some of the cases with high platelet counts large clumps of platelets were noticed, but no megalokaryocytes were observed.

Platelet Counting.—The method used at first was that described by Ottenberg and Rosenthal.[8] This method had several advantages: (1) simplicity of solution; (2) stability, and (3) the red cells were present. This is advisable, as they give an excellent check on the preparation. If the Wright and Kinnicut [9] method is used, one has only the platelets themselves, and errors are more probable.

The method recently described by Rees and E. E. Ecker [10] has also been tried, and has been found to give good results. Other

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7. Gulland, Lovell G., and Goodall, Alexander: The Block, New York, E. B. Treat & Co., 1912, p. 61.

8. Ottenberg, R., and Rosenthal, Nathan: A New and Simple Method for Counting Blood Platelets, J. A. M. A. **69**:999 (Sept. 22) 1917.

9. Wright, James Homer, and Kinnicut, Roger: A New Method of Counting the Blood Platelets for Clinical Purposes, and Some of the Results Obtained With It, J. A. M. A. **56**:1457 (May 20) 1911.

10. Rees, Maynard H., and Ecker, E. E.: An Improved Method for Counting Blood Platelets, J. A. M. A. **80**:621 (March 3) 1923.

methods have been described by Cramer,[11] Buckman,[12] Gram[13] and Kristenson.[14]

It was found more convenient to use a counting chamber of 0.02 mm. in depth rather than the usual 0.1. If the dilution was 1 to 200 and a square mm. was counted, the factor would be 1/50 × 1/200 or 1/10,000. This is, of course, too high, and was reduced by counting not less than three different preparations of 1 square mm. each.

Writers vary somewhat in their estimation of a normal count: Wood[15] suggests from 200,000 to 400,000, Webster[16] suggests 250,000, while Naegeli[17] quotes five different observers, the average being between 200,000 and 250,000. Hence, it would seem reasonable to assume that 300,000 is approximately a normal figure.

Case No.	Apparent Time Since Onset	White Blood Cells	Platelets	Neutrophils	Eosinophils	Lymphocytes	Transitionals	Leukocytes	Myelocytes	Basophils	Termination
				Before Treatment							
4	3 months	13,000	680,000	89.6	3.0	4.8	2.2	0.6	...	...	Dead
8	3½ years	11,000	400,000	47.8	7.8	34.8	7.0	1.8	0.4	0.4	Dead
5	1½ years	10,900	38,000	86.2	...	9.4	3.6	0.6	...	0.2	Dead
7	3 months	10,000	150,000	78.4	0.3	18.3	3.0	...	...	...	Living
15	6 weeks	8,800	230,000	62.0	12.0	22.0	3.7	...	...	0.3	Lost
16	4 years	7,200	210,000	69.0	0.6	26.4	3.7	...	...	0.3	Living
12	1 year	6,000	200,000	61.4	1.3	32.4	4.6	...	...	0.3	Dead
6	1½ years	4,900	150,000	67.4	2.6	26.0	3.2	...	...	0.8	Dead
17	8 months	4,200	150,000	54.4	5.0	31.3	3.0	...	...	6.3	Living
13	2 months	4,000	180,000	71.6	...	20.6	7.4	0.2	0.2	...	Dead
				After Treatment							
11	5½ years	10,000	340,000	79.6	0.2	3.0	17.0	...	...	0.2	Dead
10	5 months	8,200	350,000	71.8	2.4	17.6	7.6	...	...	0.6	Living
9	2 years	7,000	370,000	76.4	4.8	13.4	5.0	0.2	...	0.2	Living
1	1 year	6,000	560,000	78.6	3.2	6.8	11.2	...	...	0.2	Dead
2	7 months 1 year 4 months	5,700	300,000	78.0	2.2	11.2	6.6	2.0	...	...	Living
18	3 months	4,500	280,000	65.8	...	31.0	2.8	0.4	...	...	Living
3	15 months	4,300	470,000	70.8	3.8	20.0	3.6	...	0.6	1.2	Dead
14	4 months	2,000	45,000	32.5	...	62.0	5.0	0.5	...	...	Living

The table shows that in the untreated cases, only two are above this limit, while in the treated cases there are five above 300,000 and one just 300,000, but of these three are less than 400,000. Therefore,

11. Cramer, W.; Drew, A. H., and Mottram, J. C.: On Blood Platelets: Their Behavior in "Vitamin A" Deficiency and After "Radiation," and Their Relation to Bacterial Infections, Proc. Roy. Soc., B. **93**:449, 1922.

12. Buckman T. E., and Hallisey, Joseph E.: Studies in the Properties of Blood Platelets. (A New Method for Counting Platelets), J. A. M. A. **76**:427 (Feb. 12) 1921.

13. Gram, H. C.: On the Platelet Count and Bleeding Time in Diseases of the Blood, Arch. Int. Med. **25**:325 (March) 1920.

14. Kristenson, A.: New Method for Counting Blood Platelets in Man, Acta Med. Scand. **57**:301, 1922.

15. Wood, T. C.: Chemical and Microscopical Diagnosis, New York, D. Appleton and Company, 1917, p. 100.

16. Webster, Ralph W.: Diagnostic Methods, Philadelphia, P. Blakiston's Sons and Company, 1920, p. 580.

17. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Leipzig, Von Veit, 1912, p. 344.

in the eighteen cases, both treated and untreated, only seven have high platelet counts.

THE WASSERMANN REACTION

In fourteen cases, the Wassermann tests were negative, in three doubtful: Case 7, alcohol —, cholesterin + +; Case 9, never positive in both antigens, but the test was performed three times with the following results: alcohol —, cholesterin + +; alcohol + +, cholesterin —; alcohol + + +, cholesterin —; Case 15: the diagnosis was tabes, but the Wassermann test was never definite; in other words, the blood Wassermann was negative three times and doubtful twice, as follows: alcohol ±, cholesterin + +; alcohol —, cholesterin +, both after provocative doses of arsphenamin. The spinal fluid was negative twice.

In Case 4, a private patient, the Wassermann test was not performed.

Strangely enough, the treated patients show both more higher platelet counts and more increased transitionals than the untreated.

SUMMARY

1. From this series of eighteen cases, it would not be possible to diagnose Hodgkin's disease from examination of the blood.

2. In this series, platelet counts were high in seven and transitionals were high in eight.

3. It is advisable to count platelets, when possible, as estimating the number from the smear is not always reliable.

4. The length of illness apparently has no bearing on the total white count.

THE ETIOLOGIC RELATION OF ACHYLIA GASTRICA TO COMBINED SCLEROSIS OF THE SPINAL CORD

THE RELIEF OF SYMPTOMS FOLLOWING ADEQUATE HYDROCHLORIC ACID THERAPY *

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In a recent clinical study of 451 patients with achylia gastrica, there were twenty-nine with definite evidence of combined sclerosis of the spinal cord. Of these twenty-nine patients, fourteen had pernicious anemia, one had pellagra, and in seven the observations were unsatisfactory or incomplete, leaving seven patients that form the basis of this article.

SUMMARY OF THE CASES

These seven patients with combined sclerosis of the spinal cord all received complete clinical and laboratory studies. The gastric analyses were made by the fractional method, one examination being made in Cases 4, 6 and 7, two examinations in Cases 1, 2 and 5, and seven gastric analyses were made in Case 3. Blood counts were made in all cases, together with a study of the stained smears, and showed no evidence of pernicious anemia except the late developments in Case 7. The Wassermann reaction on the blood serum was negative in all cases, and the spinal fluid was examined and found normal in Cases 2, 3 and 5. The blood sugar was examined and found normal in Cases 3, 5 and 6, and the nitrogen content of the blood was found normal in Cases 3, 5, 6 and 7.

Foci of chronic infection were sought for in all cases; in Patient 7 none could be found; Patient 3 had infected tonsils which were removed; Patient 2 had a mild prostatitis which cleared up on treatment; in Cases 1, 2 and 3 there were apical abscesses about certain teeth, and these teeth were extracted; Patient 4 showed marked pyorrhea alveolaris; Patient 5 had had all of his remaining teeth extracted two months before the onset of his paresthesias, and he said that several of these teeth were abscessed; Patient 6 had lost all his teeth except four, and these showed extensive pyorrhea. There was moderate arterial hypertension in Cases 3 and 6; in the five remaining cases, the blood pressure was normal.

Treatment in each case consisted in the removal of such foci of infection as could be found, and the regular and persistent admini-

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stration of one teaspoonful of the official dilute hydrochloric acid with each meal. The acid was given in 6 or 8 ounces of water, lemonade, orangeade, iced tea or, preferably, buttermilk. The results of treatment are particularly interesting in that Patient 3 is subjectively cured; Patients 1 and 5 are apparently well, and Patient 6 is greatly improved. Patient 4 discontinued his treatment, and later wrote that he was unimproved. Patient 7 is growing progressively worse, but it is learned that he took the hydrochloric acid in inadequate amounts and later discontinued it. Patient 2 took his hydrochloric acid regularly, but died two and one-half years after his treatment was started of progressive spinal cord symptoms. A brief abstract of the histories of these seven cases follow:

REPORT OF CASES

CASE 1.—Mrs. M., married, aged 51 years, was seen on May 21, 1918, complaining of a burning, creeping sensation in the feet and legs of six months' duration. These paresthesias were worse at night and kept her from sleeping. She had had no indigestion since her gallbladder was removed in 1913, except for a morning diarrhea for the past six years. Her tongue was clean but not bald.

The patient returned for observation Jan. 4, 1919. She had taken hydrochloric acid regularly until November, 1918, and the paresthesias in the feet had improved; she then stopped the acid and the burning in the feet returned. She had then resumed the acid, but the burning sensation in the feet had persisted for some time. Her diarrhea stopped when she was first put on the hydrochloric acid and her bowels were regular until she stopped the acid, when they became loose again.

The patient was last heard from on Feb. 14, 1923, when she wrote, in response to an inquiry addressed to her home in another state, as follows: "I have taken the hydrochloric acid regularly, only leaving it off occasionally to watch the effect. I find that my feet burn if I leave it off more than two days. I still take the dose prescribed by you. I have not had a doctor since I saw you, and do not know whether I am anemic but I seem to be well."

CASE 2.—Mr. D., married, aged 65 years, a retired farmer, was first seen on March 11, 1919, complaining of numbness in the hands and feet of four months' duration. His past health had been excellent with no history of acute infections, except an attack of gonorrhea at the age of 20 years. He gave a history of sciatica ten years previously, with gradual recovery and no recurrence. His appetite was good, and he gave no history of digestive disturbance except occasional slight diarrhea and, more recently, some flatulence. He had used tobacco and liquor in moderation in the past but not in recent years. There was no loss of weight. His first symptom was numbness and tingling in the fingers and toes on the left side, with similar involvement, a few days later, on the right side. A little later he noticed numbness on the inner aspects of both thighs and then over the abdomen up to the rib margins. He had had no darting pains, no muscular weakness, no difficulty in walking in the dark and no incontinence of the sphincters. Smooth objects, like apples, felt rough to his fingers. He had observed no objective change in the extremities. The tongue was clean and distinctly red about the margins and tip.

He was next seen in October, 1919, when he said that his numbness was worse and affected the hands, forearms, feet, legs and hips. He had difficulty in picking up small objects and in writing. (He constantly rubbed the palmar

surface of the thumb of each hand against the palmar surface of the fingers.) He was a little unsteady on his feet, but he said he had no difficulty in walking. He had no pain or stiffness in his back. He had taken his hydrochloric acid regularly in teaspoonful doses with his meals. He said that he had suffered with sore tongue for years before taking this acid, but not since. He had no further diarrhea. His digestion was good. He had no urinary disturbances. The tongue was moist, red and clean.

The patient was next seen in January, 1920. He had lost 9 pounds (4.1 kg.) since March, 1919. His general condition appeared to be unchanged. The neurologic findings indicated that the trouble had been progressive.

In May, 1921, I saw the patient for the last time, at his home in a distant part of the state, and he then showed a flaccid paraplegia with marked ataxia, absent deep reflexes and involvement of the sphincters. He died in October, 1921. For three weeks prior to his death he had difficulty in swallowing and retention of urine. His family physician reported that at no time did he present any appearance of pernicious anemia, and that several blood counts made during the last few months of his life showed no reduction in either the red cell count or in the hemoglobin. It was understood that the patient took full doses of hydrochloric acid during practically the whole period of his illness.

Case 3.—Mrs. F., aged 42 years, first consulted me on Nov. 15, 1919, complaining of a sensation of numbness which began in the feet in February, 1919, and then gradually extended up the legs and trunk to the waistline. A little later she developed numbness in the hands and arms, extending up to the elbows. She said that the soles of her feet felt as if she were walking on something stiff, not like cotton. She said she had difficulty in walking, could not manage her feet well, was inclined to catch hold of things when she walked, and that she fell easily. She had difficulty in picking up small objects and in fastening her clothes and often dropped things. She said she had no tingling and no loss of touch sensation. About three years previously she had developed a sore mouth, and since then the tongue had been red and inflamed.

Her past history showed that she had had malaria at 17, diphtheria at 21, attacks of tonsillitis but none in the past eight years, and influenza in 1918. The appendix and one ovary were removed in 1904. She had had no indigestion except flatulence. The bowels were constipated. She had acute cystitis with hematuria in June, 1919. At that time she had increased blood pressure. The tongue was moist, red and clean.

The patient was again seen in May 1920; October, 1920; June, 1921; June, 1922, and March, 1923. By October, 1920, the numbness in the extremities had disappeared, except for slight paresthesia in both feet, and she had no further stomatitis. Since that time, the patient had considered herself entirely well. When last seen in March, 1923, she said she had no numbness, except occasionally when tired she might notice a feeling of sleepiness or heaviness in her feet and legs. Her appetite was splendid, and she had no indigestion. She was again completely examined, and her seventh gastric analysis showed a complete achylia. It was interesting to note that, in spite of the disappearance of subjective symptoms, the physical signs persisted. All of the deep reflexes were exaggerated; there was an exhaustible ankle clonus, and sensation to touch was greatly impaired from the feet up to a point midway from the ankle to the knee on each side. She had taken hydrochloric acid regularly since 1919, and she was advised to continue it.

Case 4.—Mr. M., a farmer, aged 60 years, married, was seen on April 13, 1920, complaining of stomach trouble and a crawling sensation in his legs. His past history included malaria in 1910, grip in 1905, and rather frequent sore throat. Otherwise it was unimportant. He had used tobacco freely, but very little liquor. He was 12 pounds (5.4 kg.) below his usual weight.

His present illness dated back one year previously, when he developed pain in the abdomen and paresthesias in the extremities. The epigastric pain was

never severe, usually occurred two or three hours after meals, and he was constipated. He had had no nausea, vomiting or flatulence and gave no history of acute pain or colics. The paresthesias were described as a peculiar crawling sensation in the legs with a burning in the feet and ankles. His tongue was clean. In response to an inquiry, the patient wrote, under date of March 14, 1923, from his home in the country that he had "not been able" to take the acid, that he continued to suffer with the burning sensation in his legs, and that his digestion was poor.

CASE 5.—Mr. M., aged 61, a lawyer, single, was seen on Nov. 28, 1921, complaining of numbness and loss of control of the legs and hands. He used to have a good deal of indigestion, and beginning in 1891 he had diarrhea with undigested food in his stools for two years. (He described a rather typical gastrogenous diarrhea.) His digestion then improved until 1914, when he again developed diarrhea and weakness. Gastric analysis at that time showed a complete achylia. (This fact was confirmed by communication with the physician who examined him at that time.) He was given small doses of hydrochloric acid but did not take it regularly. His appendix was removed in 1915, and since that time his bowels had been regular, and he regarded his digestion as good. His past history was otherwise unimportant. He smoked and drank in a moderate way.

In March, 1921, the patient had some rheumatic pains in the lower legs. All his remaining teeth were extracted in August, 1921. He said that several of these were abscessed. Early in October, 1921, he noticed a numbness and peculiar feeling in the left great toe. This numbness soon spread to the other toes and to the foot, and soon started in the same way in the right foot and gradually spread up both legs to the groins; he then developed a tight feeling about the trunk as if a cord were tied around the waist. Shortly after the onset of the paresthesias in the feet, the same numbness developed in the fingers of both sides and then spread over the hands. He complained that he did not have proper control of the arms and legs, and had difficulty in writing and in walking. He had no headache, vertigo or unconscious attacks. His mouth was not sore. He wore his shoes unlaced because of the paresthesias and was constantly rubbing his thumb and fingers together (as did Patient 2), but he had no tremors or pill-rolling motion. The tongue was clean but not bald. He was again seen on Dec. 28, 1921. His weight was the same and his general condition was unchanged, except that he said the feeling of tightness around his waist had risen a little higher on his trunk and was then noticed around the lower part of the chest.

The patient returned for examination, by request, in April, 1923. He said that he regarded himself as well and was actively engaged in his law practice. He said that the greatest improvement had occurred in his hands, in which the numbness had practically disappeared. The girdle sensation had also disappeared, together with the constricted feeling across the hips and lower abdomen. He had no difficulty in writing or in walking. He continued to be conscious of some numbness in his feet and legs. He had taken the hydrochloric acid regularly. His appetite was good; he had no indigestion or sore mouth; his bowels were regular. Examination showed that the physical signs persisted in the lower extremities with absent deep reflexes and definite loss of sensation to touch with diminished pain sense, especially over the inner aspect of the legs. Gastric analysis was repeated at this time and showed free hydrochloric acid absent at the end of thirty, forty-five and sixty minutes. Blood count showed: red cells 4,216,000; hemoglobin, 85 per cent.; differential leukocyte count and morphologic picture normal.

CASE 6.—Mr. S., aged 71, married, a farmer, was seen on June 28, 1922, complaining of intense burning in the feet of four months' duration. His past history showed that his general health had been excellent; he had had some indigestion as a younger man, characterized by sour stomach, but had had no

digestive disturbance in the past twenty years. His bowels had always been regular. He had used tobacco, but no liquor. He was underweight about 10 pounds (4.5 kg.). In the latter part of February, 1922, he suddenly developed a burning sensation in the soles of both feet, without any redness or swelling. Then he gradually developed numbness in both legs with a sensation as if water were dripping on them, and some difficulty in walking. He had also developed burning in the ends of the fingers and some burning spots on the face. The burning in the feet was distressing, and at first was constant day and night, but after taking some medicine from his home physician, he had been able to secure some sleep at night. He said that his hands felt drawn and cramped. The tongue was slightly coated.

On March 16, 1923, the patient's physician wrote: "Mr. S., asked me to reply to your letter and to say that he weighs fifteen pounds more than he has for thirty years; that he has taken his hydrochloric acid every day since he saw you, except eight days; that his feet do not burn at night but do burn some in the daytime; that he eats anything and as much as he wants." The physician added that the patient looked a good deal better and was not anemic.

Case 7.—Dr. X., aged 64, married, was first seen by a colleague on June 5, 1922, and the case has since then been followed by both of us. The patient's past health had always been good. He had had influenza in 1918 and again in 1921; otherwise he had had no illnesses and no acute infections since childhood. He had been a moderate smoker but had never used liquor. He dated the onset of his present illness to an attack of influenza in October, 1921, although he had not felt well since December, 1920, when, after some exertion, he had had a brief attack of dizziness, confusion and a feeling of prostration. About October, 1921, he began to suffer from distressing paresthesias, with numbness in the feet, legs and hands. He became nervous, anxious and irritable and had some dizziness. He had developed difficulty in using his fingers for finer movements, and his gait had become uncertain. He had had no headache or convulsive attacks, no disturbances of the special senses, and he gave no history of digestive disturbances or any loss of weight. Gastric analysis was made because of the paresthesias and evident cord changes and showed free hydrochloric acid absent at thirty and forty-five minutes after an Ewald test breakfast, after which time the stomach was found empty.

The patient was seen again on Dec. 16, 1922. He had deteriorated mentally, was restless and irritable and unable to work. He showed increasing signs of involvement of the pyramidal tracts and complained very much of paresthesia. The blood count at this time, confirmed by a second count the next day, showed a normal morphologic appearance and leukocyte count, but the color index was high, the red cells numbering 2,576,000 and the hemoglobin 70 per cent.

On April 9, 1923, it was reported that the paresthesia persisted and involved the hands, feet, legs and abdomen. He continually rubbed the thumb against the fingers. Strength was fairly good, but he showed a rather pronounced spastic paraplegia. There were no ataxia, no tremors and no cranial nerve palsies. Last year he took 30 drops of dilute hydrochloric acid with meals for several months after which he discontinued it. The blood count when examined showed: red cells 2,768,000; hemoglobin, 73 per cent., differential leukocyte count normal; no nucleated red cells, slight anisocytosis, no poikilocytosis and no basophilic degeneration.

THE PATHOLOGY AND SYMPTOMATOLOGY OF COMBINED SCLEROSIS OF THE SPINAL CORD

Combined sclerosis of the spinal cord is characterized anatomically by degenerative lesions in the posterior and lateral columns, and the affected areas are unlike those occurring in any other disease in that no neurogliar increase follows the degeneration. Collier, in his recent

monograph,[1] states that the clinical features of subacute combined degeneration of the spinal cord are usually strikingly distinct in that subjective sensations, such as tingling, numbness and burning, occurring usually at the periphery of the extremities, are early, obtrusive and persistent symptoms, and are accompanied or followed by the development of a paraplegia which may be of a spastic type, or of a flaccid and ataxic type, or of a mixed type, according to the degree of affection of the lateral and of the posterior columns in each case. The deep reflexes are present, exaggerated or absent, according to the relative condition of these columns. Loss of sensibility of peculiar distribution occurs, which has a "glove and stocking" distribution on the extremities and a segmental distribution on the trunk. In the late stages of the malady the paraplegia tends to become complete and of the flaccid type, with loss of the deep reflexes. It is a disease of adult life, most of the cases occurring in the fifth, sixth and seventh decades. The sexes are equally affected; heredity is not a factor, and syphilis plays no part in the etiology.

THE RELATION OF PERNICIOUS ANEMIA TO COMBINED SCLEROSIS OF THE SPINAL CORD

The intimate relation of pernicious anemia to combined sclerosis of the spinal cord has been emphasized by many writers,[2] and the earlier authors believed that the degeneration in the nervous system was the result of vascular changes consequent on the anemia. This point is negatived, as pointed out by Collier, by the facts that some cases of combined spinal sclerosis progress to a fatal issue without any evidence of anemia, and that in others the nervous manifestations may become severe long before any anemia is evident. Collier concludes that certain experimental evidence as well as the clinical and pathologic features of the disease suggest that the anemia and the degeneration of the nervous system are not dependent the one on the other, but that they are the concomitant but not necessarily synchronous results of one and the same cause.

ASSOCIATION OF ACHYLIA GASTRICA WITH PERNICIOUS ANEMIA

The almost invariable association of achylia gastrica with pernicious anemia has been recognized for many years. Among the more recent reports is that of Levine and Ladd,[3] who report an absence of free

1. Collier, J.: Intrinsic Diseases of the Spinal Cord, Oxford Medicine, New York, Oxford University Press, **5**:356, 1921.

2. For a good bibliography and an excellent discussion of this subject, based on a study of 150 patients at the Mayo Clinic, see article by Woltmann, H. W.: The Nervous Symptoms in Pernicious Anemia, Am. J. M. Sc. **157**:400, 1919.

3. Levine, S. A., and Ladd, W. S.: Pernicious Anemia; a Clinical Study of 150 Consecutive Cases with Special Reference to Gastric Anacidity, Bull. Johns Hopkins Hosp. **32**:254, 1921.

hydrochloric acid in the gastric contents of 104 out of 107 patients suffering from pernicious anemia. Here, again, the older writers were inclined to attribute the achlorhydria to the anemia, and the view continues to be expressed that pernicious anemia causes gastric anacidity. That such an opinion is erroneous would seem, however, to be abundantly proved by the accumulated reports in the literature of cases in which it has been shown that persistent achylia gastrica precedes by months or years the onset of pernicious anemia; also, by the fact that the achlorhydria persists throughout periods of remission in pernicious anemia; and again by the fact that there is no constant curve of gastric secretion in other forms of severe anemia, and that the most pronounced secondary anemias, as a rule, do not show achlorhydria. Finally, and this seems conclusive, pernicious anemia has subsequently developed in certain patients following the artificial achylia induced by total gastrectomy for the relief of gastric carcinoma, without evidence of recurrence of the malignant disease. Such a case has been reported from the Mayo Clinic by Hartman,[4] and five such instances are mentioned by Hurst and Bell in their article referred to below. Already certain animal experiments are under way by my colleagues, Dr. Haskell and Dr. Courtney, in the department of physiology of the Medical College of Virginia, to determine the blood changes that may follow total gastrectomy in dogs.

RELATIONSHIP OF ACHYLIA GASTRICA TO COMBINED SCLEROSIS OF THE SPINAL CORD

The relationship of achylia gastrica to pernicious anemia having been established, as well as the association of pernicious anemia with combined spinal sclerosis, it is strange that the relationship of achylia gastrica to combined spinal sclerosis was not noted long ago. Careful search of the literature failed to elicit any reference to this interesting association until recently when my attention was directed to the excellent and conclusive monograph of Arthur F. Hurst and J. R. Bell.[5] These authors report eight cases of combined spinal sclerosis, in all of which gastric analysis, by the fractional method, showed an absence of free hydrochloric acid. The test was repeated in three of the cases with the same result. They quote L. F. Barker[6] as having found complete achlorhydria in two cases of combined spinal sclerosis, and also mention

4. Hartman, H. R.: Blood Changes in a Gastrectomized Patient Simulating Those in Pernicious Anemia, Am. J. M. Sc. **162**:201, 1921.

5. Hurst, A. F., and Bell, J. R.: The Pathogenesis of Subacute Combined Degeneration of the Spinal Cord, with Special Reference to Its Connection with Addison's (Pernicious) Anemia; Achlorhydria and Intestinal Infection, Brain **45**: pt. 2, 266, 1922.

6. Barker, L. F.: Funicular Myelitis, or Combined Sclerosis of the Spinal Cord, Med. Clin. of N. America **2**:1551, 1919.

a personal communication from Dr. J. F. Wilkinson, of Melbourne, who found achlorhydria in a patient with digestive disturbances one year before the first sign of combined spinal sclerosis appeared.

For purposes of control, Hurst and Bell made gastric analyses in a series of eight consecutive cases of disseminated sclerosis and nine consecutive cases of tabes dorsalis. In these seventeen cases, achlorhydria was not found, except in one tabetic person. When the well-known frequency of achylia gastrica is considered, no special importance can be attached to this one case out of seventeen. These authors say further:

> In three recent cases, which presented features very suggestive of subacute combined degeneration, a normal curve of gastric acidity was discovered. Each eventually proved to be a case of syphilitic disease of the spinal cord. These cases are analagous with two others, the only cases in Guy's Hospital in which a diagnosis of Addison's anemia had been made in spite of the fact that free hydrochloric acid was present in the stomach. At the postmortem no evidence of hemolysis was present, one being found to have infective endocarditis, and the other, who died of lobar pneumonia, having microscopical changes in the spleen which were typical of Hodgkin's disease.

For the past several years, as indicated by the accompanying case histories, I have been greatly interested in my observation that achylia gastrica was an almost invariable finding in patients with acroparesthesias and symptoms of combined spinal sclerosis. In fact, this relationship impressed me as being as constant as the finding of achlorhydria in patients suffering from pernicious anemia. During this period, the diagnosis of combined spinal sclerosis was made in the case of one patient who showed free hydrochloric acid present in the gastric contents. This patient, however, was seen only once, and because of insufficient observation the opinion formed of his neurologic lesion was not considered conclusive. A certain proportion of persons with achylia gastrica have few, if any gastro-intestinal symptoms, and in five of the seven cases reported in this article it was the paresthesias, and not any abdominal complaint, that caused us to make the gastric analyses.

As is well known and illustrated by the case reports in this article, combined spinal sclerosis occurs in many persons who present no evidence of pernicious anemia. Woltmann [2] states that only one third of the patients suffering from subacute combined sclerosis of the spinal cord seen at the Mayo Clinic were found to have pernicious anemia, and quotes von Voss (1897) as finding about the same proportion of cases of pernicious anemia in a series of collected cases of combined spinal sclerosis. In my series of twenty-nine patients with combined spinal sclerosis, all of whom showed an achlorhydria, there were fourteen instances of unquestioned pernicious anemia. Several writers, among

them Cadwalader,[7] have shown that continued observation of patients suffering from combined spinal sclerosis will demonstrate the subsequent development of the characteristic clinical and hematologic picture of pernicious anemia in a large proportion of the cases.

THE PATHOGENESIS OF COMBINED SCLEROSIS OF THE SPINAL CORD

In the most authoritative description of subacute degeneration of the spinal cord by James Collier,[1] published as recently as 1921, it is stated that:

> Little is known of the causal factors of the disease, and in the majority of the recorded cases the patients have been strong and healthy until the onset of nervous symptoms. In a considerable number of cases, however, symptoms pointing to gastro-intestinal infection, such as vomiting, diarrhea, anorexia or constipation, have been prominent before the onset of the nervous symptoms.

The failure of clinicians to recognize the almost invariable association of achylia gastrica with combined sclerosis of the spinal cord has, no doubt, been due, as Hurst and Bell point out, to the fact that this nervous disorder has been chiefly investigated by neurologists, who were only interested in a minor degree in the associated anemia or gastro-intestinal disturbances; while, on the other hand, the spinal changes observed in pernicious anemia have been investigated chiefly by physicians, whose interest was in the anemia rather than in the spinal disease. The significant feature of the monograph of Hurst and Bell is the fact that they discuss the two groups of cases, combined spinal sclerosis and pernicious anemia, from a common standpoint, and that they endeavor to show that both depend on the same underlying pathologic processes, namely, oral sepsis, absence of free hydrochloric acid from the stomach contents throughout digestion and consequent intestinal infection and intoxication.

In spite of the expressed views of many writers who continue to reiterate the earlier confused state of our knowledge regarding the etiology of pernicious anemia, there is every reason to believe that achylia gastrica not only accompanies and precedes the development of this malady, but that it is an essential predisposing cause. The secretion of hydrochloric acid by the stomach is one of Nature's chemical defences against infection, and it is most probable that in all cases of persistent achylia gastrica there ensues, sooner or later, a chronic intestinal toxemia. This toxemia must be tolerated by many persons for long periods of time, as achlorhydria is a common finding. (My

7. Cadwalader, W. B.: Early Appearance of Symptoms of Combined Sclerosis of the Spinal Cord and Subsequent Development of Severe Anemia, Pennsylvania M. J. **24**:692, 1921.

451 cases of achylia gastrica occurred in a series of 4,281 consecutive private patients subjected to gastric analysis, thus showing an incidence of 10.5 per cent.)

In other persons, however, toxins are evidently produced either from bacterial decomposition of the food that enters the intestines unprepared by the usual gastric digestion, or from bacteria from the mouth and throat that pass through the achylous stomach uninhibited by the acidity of the normal gastric juice. Of such toxins, one variety may have an especial affinity for the bone marrow or other hemopoietic organs and give rise to a hemolytic form of anemia, while another may exert its effect on the nervous tissues with a point of vulnerability in the posterior and lateral columns of the spinal cord. In one person the hemolytic toxin predominates, in another patient the neurotoxin is chiefly manifested, while in not a few cases there is evidence of a reaction to both toxins, as is seen in the advanced case of pernicious anemia with cord changes.

The chief significance of this report of certain cases of combined sclerosis of the spinal cord associated with achylia gastrica, confirming abundantly the published findings of Hurst and Bell, is that it would seem to shed considerable light on the etiology of pernicious anemia. In combined spinal sclerosis we also find achlorhydria as an essential predisposing cause, a most constant factor that is lacking in certain other degenerative lesions of the spinal cord, such as disseminated sclerosis and tabes dorsalis. In fact, as Hurst and Bell emphasize, the presence of free hydrochloric acid in any fraction of a test meal is probably a decisive point against the diagnosis of combined spinal sclerosis in a doubtful case. The frequent association of combined sclerosis of the spinal cord and pernicious anemia would indicate that the absence of the protective power of the normal gastric juice may permit the elaboration of both a neurotoxin and a hemolytic toxin. Hence, combined spinal sclerosis and pernicious anemia may coexist in the same patient, or either disease may arise separately, depending on the character and amount of the toxins produced.

Many writers, especially those from Guy's Hospital, where Addison reported the first recorded cases of pernicious anemia, have emphasized the presence of oral sepsis in this disease ever since Hunter first drew attention to the subject over twenty years ago. Alveolar infection was noted in all of the eight cases of achlorhydria and combined spinal sclerosis reported by Hurst and Bell, and reference to my present cases shows that infection about the teeth was present in six of the seven patients. In this connection it may be significant to note that Hurst and Bell recovered a streptococcus from the duodenum with the Einhorn

tube in seven consecutive cases of pernicious anemia and in four consecutive cases of combined spinal sclerosis, while the same organism was recovered in only three out of twenty-six control cases.

PROGNOSIS IN PERNICIOUS ANEMIA AND IN COMBINED SCLEROSIS OF THE SPINAL CORD

A point that should be emphasized is that true achylia gastrica is a persistent and probably permanent condition. I have had under frequent observation a woman, now 52 years old, in whom I first found an achlorhydria in January, 1909, and in whom fifteen consecutive gastric analyses in the intervening years have continued to show the absence of free hydrochloric acid. This patient has taken dilute hydrochloric acid in teaspoonful doses with meals regularly for the past fourteen years and has never shown any anemia or spinal cord changes. In common with all other clinicians, however, pernicious anemia has continued to be a fatal disease in my observation, with the possible exception of one most interesting patient who had an achylia gastrica in 1914, again in 1917, associated with a characteristic picture of pernicious anemia, intensive hydrochloric acid therapy since 1917, and a normal blood picture in 1923, although the achylia gastrica persists.

The outlook in cases of combined spinal sclerosis unassociated with pernicious anemia has impressed me as being much more favorable, that is, in those cases in which the achylia gastrica is recognized and appropriate treatment instituted. As mentioned in the foregoing, among the seven patients that form the basis of this article, one is subjectively cured, two are apparently well and one is greatly improved. These subjective results are particularly interesting in that the degenerative lesions in the spinal cord are probably permanent, and the physical signs persist or gradually recede. Hurst and Bell state that sufficient time had not elapsed at the time of their publication to report the final results of treatment, but that in two of their cases there had been no increase in the nervous symptoms, and that in one of these patients the tingling of the feet and hands had almost disappeared and the ataxic and spastic gait had greatly improved, although the physical signs were unaltered.

These results in the expected outcome in combined sclerosis of the spinal cord are in striking contrast to the former views on this subject. In fact, Collier, in his authoritative monograph already referred to, writes in 1921, that "There is no evidence that recovery from this disease occurs in any of its stages."

Taking into consideration all the various factors already enumerated, I am firmly convinced that every person suffering from achylia gastrica

has a potential case of either pernicious anemia or combined sclerosis of the spinal cord. I am equally convinced that treatment, while encouraging in patients having paresthesias and symptoms of pyramidal tract degeneration without anemia, finds its greatest usefulness as a prophylactic measure. In other words, every person with an achlorhydria should receive regular and adequate amounts of hydrochloric acid with every meal, and this remedy should not be omitted or discontinued unless it can be shown by a subsequent gastric analysis that the stomach has renewed its secretory activity.

TREATMENT OF COMBINED SCLEROSIS OF THE SPINAL CORD AND THE ASSOCIATED ACHYLIA GASTRICA

The essential part of the treatment in every patient with achylia gastrica is the artificial replacement of the hydrochloric acid secretion in the stomach. This is readily accomplished by administering dilute hydrochloric acid with each meal. The matter of dosage is of much importance, and the pharmacopeal recommendation of 10 to 15 minims (0.6 to 0.9 c.c.) is obsolete and entirely inadequate. For the past fifteen years it has been my custom to order one teaspoonful of the official dilute hydrochloric acid, well diluted, with each meal, and after the introduction of the duodenal tube in making routine gastric analyses by the fractional method, I satisfied myself, experimentally, that this dose was sufficient. In certain cases, however, in addition to one teaspoonful of the acid with meals, I have ordered a second teaspoonful to be taken one-half hour after the meal. Hurst and Bell reproduce certain charts to illustrate that a dram and a half (5.85 gm.) of dilute hydrochloric acid are required in order to compensate for the deficiency of gastric juice, and state that the acid should be added in the proportion of 1 dram (3.9 gm.) to 4 ounces (124.4 gm.) of water in order to make a beverage, the acidity of which is about the same as that of gastric juice. The acid is best administered in buttermilk, but may be taken in sweetened lemonade or orangeade, or in iced tea. It is a rather unpleasant dose in plain water. The acid-containing beverage is sipped during the course of the meal, and part of it may be reserved for the twenty or thirty minute period following the meal. The administration of pepsin, pancreatin or other digestive ferments, while quite appropriate, has never appeared to be of any special value, and I rarely employ them in these cases. I have found that it is advisable to prohibit eating between meals except for indulgence in acid fruits, which may be taken freely. Buttermilk, either the natural article or milk which has been artificially soured with lactic acid bacilli, may also be taken at any time, and is not only well tolerated in cases of achlorhydria, but seems also to be particularly helpful.

Chronic foci of infection should always be sought for and eradicated if possible. Chronic infection in the gallbladder is a rather frequent associated lesion in patients with achlorhydria. Chronic cholecystitis was diagnosed in forty-nine of my 451 achylia cases, an incidence of 10.8 per cent., and was suspected in certain additional cases. Infection about the teeth and in the tonsils and accessory nasal sinuses, chronic appendicitis and chronic infection in the urinary tract are frequently to be found, and the possible special significance of oral sepsis has been emphasized above.

In combined sclerosis of the spinal cord, with the exception of the control of the associated achlorhydria, the treatment is purely symptomatic. Massage and graduated exercises may be employed, and sedatives may be used if necessary. Special treatment directed toward an accompanying anemia will not be discussed here, except to emphasize again that every person with a true achylia gastrica has a potential case of either pernicious anemia or combined sclerosis of the spinal cord, and that adequate treatment with hydrochloric acid in such instances is a prophylactic measure of the greatest value in combating the hemolytic toxins and neurotoxins that sooner or later become manifest in probably every case.

SUMMARY

In a study of 451 consecutive cases of achlorhydria, there were twenty-nine persons with definite evidence of combined sclerosis of the spinal cord. Of these twenty-nine patients, fourteeen had pernicious anemia, one had pellagra and in seven the observations were incomplete, leaving seven patients that form the basis of this report.

Combined sclerosis of the spinal cord has been regarded as a disease of obscure etiology and hopeless prognosis. The study of these seven cases would seem to show, however, that achlorhydria not only precedes and accompanies the development of this nervous disorder, but that it is in all probability an essential predisposing cause. Achylia gastrica thus appears to be as constant a finding in combined spinal sclerosis as in pernicious anemia. In one instance neurotoxins, in the other hemolytic toxins, are evidently produced in the intestinal tract of the person whose stomach lacks the protective or inhibitory action of the normal hydrochloric acid secretion.

The prognosis in patients suffering from combined sclerosis of the spinal cord, not accompanied by pernicious anemia, appears to be favorably influenced by persistent treatment with full doses of hydrochloric acid, together with the removal of such foci of chronic infection as may be found. Of the seven patients discussed in this report, one is subjectively cured, two are apparently well, and one is greatly

improved. There is good reason to believe that every person with true achylia gastrica has a potential case of either pernicious anemia or combined spinal sclerosis. More emphasis should be placed on the importance of adequate hydrochloric acid therapy as an essential prophylactic measure in every case of achylia gastrica.

BOOK REVIEWS

RECOVERY RECORD FOR USE IN TUBERCULOSIS. By GERALD B. WEBB, M.D., President, Colorado School of Tuberculosis, and CHARLES T. RYDER, M.D. Cloth. Price $2.00. Pp. 80 with 100 record forms attached. New York: Paul B. Hoeber, Inc., 1923.

Carefully written, optimistic throughout, admirably compiled, brief, accurate in its statements, none of which are so technical or involved as not to be easily comprehended by the average patient, and particularly offering a reasonable common sense explanation for each and every suggestion made, this volume should be helpful to both patient and physician.

Any intelligent tuberculous patient would profit greatly by reading this book, and every patient who is being treated at home should have the opportunity to read and reread its contents. The latter portion consists of weekly record charts for recording the temperature, pulse rate, weight, general notes, and questions to ask the physician during his visits. There are enough of these charts to cover a period of two years.

ENVIRONMENT AND RESISTANCE IN TUBERCULOSIS. By ALLEN K. KRAUSE, A.M., M.D., Editor-in-chief, The American Review of Tuberculosis. Cloth, semi-flexible. Price, $1.50. Pp. 144. Baltimore: Williams & Wilkins Company, 1923.

This book is divided into two sections: one on environment, the other on resistance. The first section—that on environment—is the revision of an address delivered in 1920 and published in the *American Review of Tuberculosis* in the same year. It was originally prepared as part of a symposium on the topic "The Basic Cause of Breakdown with Tuberculosis: Is it Malnutrition? Is it Heredity? Is it Environment?" The study of environment as an etiologic and determining factor in the development or progress of tuberculosis in an individual or community is discussed from the standpoint of nutrition, hygiene, occupation, family and social status, influence of trauma, intercurrent disease, both acute and chronic, political and racial environment, etc.

The major portion of the test is devoted to the subject of "Resistance," and, likewise, is an elaboration of several addresses on "The Nature of Resistance to Tuberculosis," all of which have been published in the *American Review of Tuberculosis* or the *Journal of the Outdoor Life*. Specific and nonspecific factors concerned in resistance are thoroughly discussed. In the first group the subject of allergy in tuberculosis is presented clearly and concisely, while in the second group the question of the nature, etc., of the tubercle, as well as the influence of "accidental factors," are considered from various angles.

Physicians and others interested in the study and treatment of tuberculosis will find the author's presentation of these important topics thorough and original.

INDEX TO VOLUME 32

PAGE

Achlorhydria and gastric ulcer; J. R. Bell 663
Achylia gastrica, etiologic relation of, to combined sclerosis of spinal cord; relief of symptoms following adequate hydrochloric acid therapy; D. Vanderhoof 958
Adkinson, J., Walker, I. C., and Wetmore, A. S.: Sensitization tests with digestive products of protein 323
Alkalis, effect of, on gastric secretion and motility; B. C. Lockwood and H. G. Chamberlin 74
Allergy: See Susceptibility
Alvarez, W. C.: Blood pressures in 15,000 university freshmen 17
Anemia, pernicious, metabolic studies in; R. B. Gibson and C. P. Howard .. 1
Ascitic fluid: See Effusions
Auricular fibrillation, clinical observations on dynamics of ventricular systole; auricular fibrillation; L. N. Katz and H. S. Feil 672

Bacteriophage in treatment of infections; E. B. McKinley 899
Bargen, J. A.: Experimental infectious streptococcus endocarditis and its arsenical therapy (sodium cacodylate) 727
Bell, J. R.: Gastric ulcer and achlorhydria 663
Blankenhorn, M. A.: Causes of turbidity in milky ascitic fluids 140
Chylous and pseudochylous effusions 129
Bloedorn, W. A., and Roberts, L. J.: Value of electrocardiograph in prognosis 718
Blood coagulation, new method for accurately determining time of; M. F. Petersen and C. A. Mills 188
concentration changes in extensive superficial burns; F. P. Underhill, G. L. Carrington, R. Kapsinow and G. T. Pack 31
pressures in 15,000 university freshmen; W. C. Alvarez 17
sugar reaction following intravenous injection of glucose; L. G. Rigler and H. L. Ulrich 343
uric acid in, relationship of excess of, to eczema and allied dermatoses, based on an analysis of over 200 cases; J. F. Schamberg and H. Brown 203
Bloomfield, A. L., and Felty, A. R.: Bacteriologic observations on acute tonsillitis with reference to epidemiology and susceptibility 483
Definition of hemolytic streptococcus parasitism in upper air passages of healthy people 386
Blumgart, H. L.: Three fatal adult cases of malabsorption of fat, with emaciation and anemia, and in two acidosis and tetany 113
Book Reviews:
Environment and Resistance in Tuberculosis; A. K. Krause 972
Recovery Record for Use in Tuberculosis; G. B. Webb and C. T. Ryder .. 972
Branch, A., and Miller, C. P.: Subacute bacterial endocarditis due to hemolytic hemophilic bacillus 911
Breath sounds, mechanism of production of; P. Martini 313
Brill, N. E., and Rosenthal, N.: Treatment by splenectomy of essential thrombocytopenia (purpura hemorrhagica) 939
Brown, G. E., and others: Toxic nephritis in pyloric and duodenal obstruction, renal insufficiency complicating gastric tetany 425

PAGE

Brown, H., and Schamberg, J. F.: Relationship of excess of uric acid in blood to eczema and allied dermatoses, based on an analysis of over 200 cases 203
Burns, blood concentration changes in extensive superficial burns; F. P. Underhill, G. L. Carrington, R. Kapsinow and G. T. Pack 31
Byfield, A. F., and Gatewood, L. C.: Clinical report on acute cases of mercuric chlorid poisoning 456

Calcareous degeneration, some interesting cases of, found in thorax; J. S. Pritchard 259
Cardiovascular system, clinical and roentgenologic study of 105 cases of syphilis with reference to cardiovascular system; E. Steinfield, G. E. Pfahler and J. V. Klauder 556
Carrington, G. L., and others: Blood concentration changes in extensive superficial burns, and their significance for systemic treatment 31
Chamberlin, H. G., and Lockwood, B. C.: Effect of alkalis on gastric secretion and motility as measured by fractional gastric analysis 74
Child, C. M.: General relation between susceptibility and physiologic condition 647
Childs, M. C. C., and Rabinowitch, I. M.: Contribution to biochemistry and treatment of chronic nephrosis (Epstein) 758
Clarkson, S., and Newburgh, L. H.: Renal injury produced in rabbits by diets containing meat 850
Coronary arteries, electrocardiographic changes following occlusion of left coronary artery; F. M. Smith 497
Cunningham, W. F., and McAlpin, K.: Experiments with Hodgkin's disease, an attempt to produce it in anthropoids and other monkeys 353

Delprat, G. D., Jr.: Studies on liver function, rose bengal elimination from blood as influenced by liver injury 401
Dermatoses, relationship of excess of uric acid in blood to eczema and allied dermatoses, based on an analysis of over 200 cases; J. F. Schamberg and H. Brown 203
Diabetes insipidus, observations on influence of pituitary extract on metabolism in diabetes insipidus; J. F. Weir 617
mellitus, blood oxygen in; S. B. Grant 764
mellitus, effects of insulin in; I. M. Rabinowitch 796
mellitus, studies of; results of treatment by diet adjustment with reference to maintenance requirement and ketogenic-antiketogenic balance; W. S. McCann, R. R. Hannon, W. A. Perlzweig and E. H. Tompkins 226
Digitalis elimination; H. Gold 779
Downey, H., and McKinlay, C. A.: Acute lymphadenosis compared with acute lymphatic leukemia 82
Duke, W. W.: Specific tests in diagnosis of allergy 298

Eczema, relationship of excess of uric acid in blood to eczema and allied dermatoses, based on an analysis of over 200 cases; J. F. Schamberg and H. Brown 203
Effusions, causes of turbidity in milky ascitic fluids; M. A. Blankenhorn .. 140
chylous and pseudocylous effusions, report of 7 cases; M. A. Blankenhorn 129
Electrocardiograph in prognosis; W. A. Bloedorn and L. J. Roberts 718
changes following occlusion of left coronary artery; F. M. Smith 497
Endocarditis, experimental infectious streptococcus endocarditis and its arsenical therapy; J. A. Bargen 727

Endocarditis—Continued PAGE
subacute bacterial, due to hemolytic hemophilic bacillus, report of case; C. P. Miller and A. Branch 911
Eusterman, G. B., and others: Toxic nephritis in pyloric and duodenal obstruction, renal insufficiency complicating gastric tetany 425
Exercise, studies on rabbit's heart; effect of vigorous exercise on size of normal and abnormal heart; B. Gordon and G. F. Strong 517

Fat, malabsorption of, three fatal adult cases with emaciation and anemia, and in two acidosis and tetany; H. L. Blumgart 113
Feil, H. S., and Katz, L. N.: Clinical observations on dynamics of ventricular systole; auricular fibrillation 672
Felty, A. R., and Bloomfield, A. L.: Bacteriologic observations on acute tonsillitis with reference to epidemiology and susceptibility 483
Definition of hemolytic streptococcus parasitism in upper air passages of healthy people 386
Forster, N. K., and Phifer, F. M.: Gonorrheal myelitis 530
Foster, J. H., and Hsieh, P. L.: Vital capacity of Chinese 335
Friedman, J. C., and Strauss, S.: Observations on changes in size and shape of hearts during progress of compensation 601
Frothingham, C., and Wolbach, S. B.: Influenza epidemic at Camp Devens in 1918 571

Garbat, A. L.: Gastric secretion in response to duodenal feeding 771
Gastroscopy in 30 cases of gastric neoplasm; R. Schindler 635
Gatewood, L. C., and Byfield, A. F.: Clinical report on acute cases of mercuric chlorid poisoning 456
Giardia infection: See Lambliasis
Gibson, R. B., and Howard, C. P.: Metabolic studies in pernicious anemia .. 1
Glucose, blood sugar reaction following intravenous injection of; L. G. Rigler and H. L. Ulrich 343
Goiter, exophthalmic, observations on 192 consecutive days of basal metabolism, food intake, pulse rate, and body weight in a patient with exophthalmic goiter; C. C. Sturgis 50
Gold, H.: Digitalis elimination 779
Gonorrheal myelitis; F. M. Phifer and N. K. Forster 530
Gordon, B., and Strong, G. F.: Studies on rabbit's heart; effect of strophanthin on size of normal and of abnormal heart 510
Studies on rabbit's heart; effect of vigorous exercise on size of normal and abnormal heart 517
Grant, S. B.: Study of blood oxygen in diabetes mellitus 764

Haden, R. L.: Elective localization in eye of bacteria from infected teeth .. 828
Hannon, R. R., and others: Studies of diabetes mellitus; results of treatment by diet adjustment with reference to maintenance requirement and ketogenic-antiketogenic balance 226
Hartman, H. R., and others: Toxic nephritis in pyloric and duodenal obstruction, renal insufficiency complicating gastric tetany 425
Heart, dynamics of ventricular systole; auricular fibrillation; L. N. Katz and H. S. Feil 672
electrocardiograph in prognosis; W. A. Bloedorn and L. J. Roberts 718
electrocardiographic changes following occlusion of left coronary artery; F. M. Smith 497
induction of premature contractions and auricular fibrillation by forced breathing, associated with a change in location of pacemaker; F. M. Smith and W. B. Moody 192

Heart—Continued PAGE
observations on changes in size and shape of hearts during progress of compensation; J. C. Friedman and S. Strauss..... 601
size of, in pneumonia, a teleroentgenographic study, with observations on effect of digitalis therapy; R. L. Levy..... 359
studies on rabbit's heart; effect of strophanthin on size of normal and of abnormal heart; G. F. Strong and B. Gordon..... 510
studies on rabbit's heart; effect of vigorous exercise on size of normal and abnormal heart; B. Gordon and G. F. Strong..... 517
Hodgkin's disease, blood counts in; report of cases; K. R. McAlpin..... 954
experiments with; attempt to produce it in monkeys; W. F. Cunningham and K. McAlpin..... 353
malignant lymphoma, a radiographic study; L. R. Whitaker..... 538
Hollander, E.: Giardia intestinalis infection..... 522
Howard, C. P., and Gibson, R. B.: Metabolic studies in pernicious anemia 1
Hsieh, P. L., and Foster, J. H.: Vital capacity of Chinese..... 335
Hypertension, observations on salt in vascular hypertension; J. P. O'Hare and W. G. Walker..... 283

Infection, bacteriophage in treatment of; E. B. McKinley..... 899
elective localization in eye of bacteria from infected teeth; R. L. Haden.. 828
staphylococcus focal, complications of; L. M. Morris..... 746
Influenza epidemic at Camp Devens in 1918; study of pathology of fatal cases; S. B. Wolbach and C. Frothingham..... 571
Insulin in treatment of diabetes mellitus; I. M. Rabinowitch..... 796
Intestines, obstruction, toxic nephritis in pyloric and duodenal obstruction, renal insufficiency complicating gastric tetany; G. E. Brown, G. B. Eusterman, H. R. Hartman and L. G. Rowntree..... 425

Kantor, J. L.: Lamblia (Giardia) infection associated with cholecystitis.. 693
Kapsinow, R., and others: Blood concentration changes in extensive superficial burns, and their significance for systemic treatment..... 31
Katz, L. N., and Feil, H. S.: Clinical observations on dynamics of ventricular systole; auricular fibrillation..... 672
Kemp, J. E., and Moore, J. E.: Studies in familial neurosyphilis; conjugal neurosyphilis 464
Kidney efficiency, urea concentration factor in estimation of; I. M. Rabinowitch 927
function, benzoate test for; F. B. Kingsbury..... 175
injury produced in rabbits by diets containing meat; L. H. Newburgh and S. Clarkson..... 850
Kingsbury, F. B.: Benzoate test for renal function..... 175
Klauder, J. V., Steinfield, E., and Pfahler, G. E.: Clinical and roentgenologic study of 105 cases of syphilis with reference to cardiovascular system 556

Lambliasis; E. Hollander..... 522
associated with cholecystitis, report of case treated with neo-arsphenamin; J. L. Kantor..... 693
Lennox, W. G., and Means, J. H.: Study of basal and nitrogenous metabolism in case of acute leukemia during roentgen-ray treatment.... 705
Leukemia, acute lymphatic, compared with acute lymphadenosis; H. Downey and C. A. McKinlay..... 82
acute, basal and nitrogenous metabolism in case during roentgen-ray treatment; W. G. Lennox and J. H. Means.....705

PAGE

Levy, R. L.: Size of heart in pneumonia, a teleroentgenographic study, with observations on effect of digitalis therapy..... 359
Liver function, studies on; rose bengal elimination from blood as influenced by liver injury; G. D. Delprat, Jr..... 401
Lockwood, B. C., and Chamberlin, H. G.: Effect of alkalis on gastric secretion and motility as measured by fractional gastric analysis..... 74
Lymphadenosis, acute, compared with acute lymphatic leukemia; H. Downey and C. A. McKinlay..... 82
Lymphoma, malignant: See Hodgkin's disease

McAlpin, K. R.: Blood counts in Hodgkin's disease..... 954
—and Cunningham, W. F.: Experiments with Hodgkin's disease, an attempt to produce it in anthropoids and other monkeys..... 353
McCann, W. S., and others: Studies of diabetes mellitus; results of treatment by diet adjustment with reference to maintenance requirement and the ketogenic-antiketogenic balance..... 226
McKinlay, C. A., and Downey, H.: Acute lymphadenosis compared with acute lymphatic leukemia..... 82
McKinley, E. B.: Bacteriophage in treatment of infections..... 899
Marine, D.: Importance of our knowledge of thyroid physiology in control of thyroid diseases..... 811
Martini, P.: Mechanism of production of breath sounds..... 313
Means, J. H., and Lennox, W. G.: Study of basal and nitrogenous metabolism in case of acute leukemia during roentgen-ray treatment..... 705
Meat, renal injury produced in rabbits by diets containing meat; L. H. Newburgh and S. Clarkson..... 850
Melanuria without melanosarcoma, report of case; J. P. Peters..... 709
Mercuric chlorid poisoning, clinical report on acute cases of; L. C. Gatewood and A. F. Byfield..... 456
Metabolism, basal and nitrogenous, in case of acute leukemia during roentgen-ray treatment; W. G. Lennox and J. H. Means..... 705
basal, during pregnancy and puerperium; H. F. Root and H. K. Root.. 411
basal, observations on 192 consecutive days in a patient with exophthalmic goiter; C. C. Sturgis..... 50
in diabetes insipidus, influence of pituitary extract on; J. F. Weir..... 617
in pernicious anemia; R. B. Gibson and C. P. Howard..... 1
Miller, C. P., and Branch, A.: Subacute bacterial endocarditis due to hemolytic hemophilic bacillus..... 911
Mills, C. A., and Petersen, M. F.: New method for accurately determining clotting time of blood..... 188
Moody, W. B., and Smith, F. M.: Induction of premature contractions and auricular fibrillation by forced breathing, associated with a change in location of pacemaker..... 192
Moore, J. E., and Kemp, J. E.: Studies in familial neurosyphilis; conjugal neurosyphilis 464
Morris, L. M.: Complications of staphylococcus focal infections..... 746
Myelitis, gonorrheal; F. M. Phifer and N. K. Forster..... 530

Nephritis, toxic, in pyloric and duodenal obstruction, renal insufficiency complicating gastric tetany; G. E. Brown, G. B. Eusterman, H. R. Hartman and L. G. Rowntree..... 425
Nephrosis, chronic, (Epstein), biochemistry and treatment of; I. M. Rabinowitch and M. C. C. Childs..... 758

PAGE

Neurosyphilis, familial, studies in; conjugal neurosyphilis (second communication); J. E. Moore and J. E. Kemp 464
Newburgh, L. H., and Clarkson, S.: Renal injury produced in rabbits by diets containing meat 850

O'Hare, J. P., and Walker, W. G.: Salt in vascular hypertension 283
Ophüls, W.: Periarteritis acuta nodosa 870

Pack, G. T., and others: Blood concentration changes in extensive superficial burns, and their significance for systemic treatment 31
Periarteritis acuta nodosa: W. Ophüls 870
Perlzweig, W. A., and others: Studies of diabetes mellitus; results of treatment by diet adjustment with reference to maintenance requirement and ketogenic-antiketogenic balance 226
Peters, J. P.: Melanuria without melanosarcoma 709
Petersen, M. F., and Mills, C. A.: New method for accurately determining clotting time of blood 188
Pfahler, G. E., Klauder, J. V., and Steinfield, E.: Clinical and roentgenologic study of 105 cases of syphilis with reference to cardiovascular system 556
Phifer, F. M., and Forster, N. K.: Gonorrheal myelitis 530
Pituitary extract, influence of, on metabolism in diabetes insipidus; J. F. Weir 617
Pneumonia, size of heart in pneumonia, a teleroentgenographic study, with observations on effect of digitalis therapy; R. L. Levy 359
Pregnancy, basal metabolism during pregnancy and puerperium; H. F. Root and H. K. Root 411
Pritchard, J. S.: Some interesting cases of calcareous degeneration found in thorax 259
Protein, clinical method for estimation of, in urine and other body fluids; M. C. Shevky and D. D. Stafford 222
sensitization tests with digestive products of; I. C. Walker, A. S. Wetmore and J. Adkinson 323
Puerperium, basal metabolism during pregnancy and; H. F. Root and H. K. Root 411
Purpura hemorrhagica, treatment by splenectomy of essential thrombocytopenia; N. E. Brill and N. Rosenthal 939

Rabinowitch, I. M.: Effects of insulin in treatment of diabetes mellitus .. 796
Urea concentration factor in estimation of renal efficiency 927
—and Childs, M. C. C.: Contribution to biochemistry and treatment of chronic nephrosis (Epstein) 758
Respiration, forced, induction of premature contractions and auricular fibrillation by forced breathing, associated with a change in location of pacemaker; F. M. Smith and W. B. Moody 192
mechanism of production of breath sounds; P. Martini 313
vital capacity of Chinese; J. H. Foster and P. L. Hsieh 335
Respiratory tract, definition of hemolytic streptococcus parasitism in upper air passages of healthy people; A. L. Bloomfield and A. R. Felty .. 386
Rigler, L. G., and Ulrich, H. L.: Blood sugar reaction following intravenous injection of glucose 343
Roberts, L. J., and Bloedorn, W. A.: Value of electrocardiograph in prognosis 718

PAGE

Root, H. F., and Root, H. K.: Basal metabolism during pregnancy and puerperium 411
Root, H. K., and Root, H. F.: Basal metabolism during pregnancy and puerperium 411
Rosenthal, N., and Brill, N. E.: Treatment by splenectomy of essential thrombocytopenia (purpura hemorrhagica) 939
Rowntree, L. G.: Water intoxication 157
—and others: Toxic nephritis in pyloric and duodenal obstruction, renal insufficiency complicating gastric tetany 425

Schamberg, J. F., and Brown, H.: Relationship of excess of uric acid in blood to eczema and allied dermatoses, based on an analysis of over 200 cases 203
Schindler, R.: Gastroscopy in 30 cases of gastric neoplasm 635
Sclerosis, combined spinal, etiologic relation of achylia gastrica to; D. Vanderhoof 958
Shevky, M. C., and Stafford, D. D.: Clinical method for estimation of protein in urine and other body fluids 222
Smith, F. M.: Electrocardiographic changes following occlusion of left coronary artery 497
—and Moody, W. B.: Induction of premature contractions and auricular fibrillation by forced breathing, associated with a change in location of pacemaker 192
Splenectomy in treatment of essential thrombocytopenia; N. E. Brill and N. Rosenthal 939
Stafford, D. D., and Shevky, M. C.: Clinical method for estimation of protein in urine and other body fluids 222
Steinfield, E., Pfahler, G. E., and Klauder, J. V.: Clinical and roentgenologic study of 105 cases of syphilis with reference to cardiovascular system 556
Stomach secretion and motility, effect of alkalis on; B. C. Lockwood and H. G. Chamberlin 74
secretion in response to duodenal feeding; A. L. Garbat 771
tumor, gastroscopy in 30 cases; R. Schindler 635
ulcer and achlorhydria; J. R. Bell 663
Strauss, S., and Friedman, J. C.: Observations on changes in size and shape of hearts during progress of compensation 601
Streptococcus endocarditis, experimental infections, and its arsenical therapy 727
hemolytic, parasitism of, in upper air passages of healthy people; A. L. Bloomfield and A. R. Felty 386
Strong, G. F., and Gordon, B.: Studies on rabbit's heart; effect of strophanthin on size of normal and of abnormal heart 510
Studies on rabbit's heart; effect of vigorous exercise on size of normal and abnormal heart 517
Strophanthin, effect of, on size of normal and of abnormal rabbit's heart; G. F. Strong and B. Gordon 510
Sturgis, C. C.: Observations on 192 consecutive days of basal metabolism, food intake, pulse rate, and body weight in a patient with exophthalmic goiter 50
Susceptibility and physiologic condition; C. M. Child 647
elective localization in eye of bacteria from infected teeth; R. L. Haden 828
sensitization tests with digestive products of protein; I. C. Walker, A. S. Wetmore and J. Adkinson 323

Susceptibility—Continued PAGE
specific tests in diagnosis of allergy; W. W. Duke..... 298
Syphilis, clinical and roentgenologic study of 105 cases with reference to cardiovascular system; E. Steinfield, G. E. Pfahler and J. V. Klauder 556

Teeth, infected, elective localization in eye of bacteria from; R. L. Haden 828
Thorax, some interesting cases of calcareous degeneration found in thorax; J. S. Pritchard..... 259
Thyroid diseases, importance of our knowledge of thyroid physiology in control of; D. Marine..... 811
Tompkins, E. H., and others: Studies of diabetes mellitus; results of treatment by diet adjustment with reference to maintenance requirement and ketogenic-antiketogenic balance..... 226
Tonsillitis, acute, bacteriologic observations on, with reference to epidemiology and susceptibility; A. L. Bloomfield and A. R. Felty..... 483

Ulrich, H. L., and Rigler, L. G.: Blood sugar reaction following intravenous injection of glucose..... 343
Underhill, F. P., and others: Blood concentration changes in extensive superficial burns, and their significance for systemic treatment..... 31
Urea concentration factor in estimation of renal efficiency; I. M. Rabinowitch 927

Vanderhoof, D.: Etiologic relation of achylia gastrica to combined sclerosis of spinal cord..... 958
Vital capacity of Chinese; an occupational study; J. H. Foster and P. L. Hsieh 335

Walker, I. C., Wetmore, A. S., and Adkinson, J.: Sensitization tests with digestive products of protein..... 323
Walker, W. G., and O'Hare, J. P.: Salt in vascular hypertension..... 283
Water intoxication; L. G. Rowntree..... 157
Weir, J. F.: Observations on influence of pituitary extract on metabolism in diabetes insipidus..... 617
Wetmore, A. S., Adkinson, J., and Walker, I. C.: Sensitization tests with digestive products of protein..... 323
Whitaker, L. R.: Malignant lymphoma (Hodgkin's disease)..... 538
Wolbach, S. B., and Frothingham, C.: Influenza epidemic at Camp Devens in 1918 571

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CONTENTS

PAGE

THE IMPORTANCE OF OUR KNOWLEDGE OF THYROID PHYSIOLOGY IN THE CONTROL OF THYROID DISEASES. DAVID MARINE, M.D., NEW YORK 811

ELECTIVE LOCALIZATION IN THE EYE OF BACTERIA FROM INFECTED TEETH. RUSSELL L. HADEN, M.D., KANSAS CITY, MO. 828

RENAL INJURY PRODUCED IN RABBITS BY DIETS CONTAINING MEAT. L. H. NEWBURGH, M.D., AND SARAH CLARKSON, M.S., ANN ARBOR, MICH. 850

PERIARTERITIS ACUTA NODOSA. W. OPHÜLS, SAN FRANCISCO. 870

THE BACTERIOPHAGE IN THE TREATMENT OF INFECTIONS. EARL B. MCKINLEY, M.D., DALLAS, TEXAS 899

SUBACUTE BACTERIAL ENDOCARDITIS DUE TO A HEMOLYTIC HEMOPHILIC BACILLUS: REPORT OF A CASE. C. PHILIP MILLER, M.D., AND ARNOLD BRANCH, M.D., NEW YORK. 911

THE UREA CONCENTRATION FACTOR IN THE ESTIMATION OF RENAL EFFICIENCY. I. M. RABINOWITCH, M.D., MONTREAL, CANADA 927

TREATMENT BY SPLENECTOMY OF ESSENTIAL THROMBOCYTOPENIA (PURPURA HEMORRHAGICA). N. E. BRILL, M.D., AND N. ROSENTHAL, M.D., NEW YORK. 939

BLOOD COUNTS IN HODGKIN'S DISEASE: REPORT OF A CASE. KENNETH R. MCALPIN, M.D., NEW YORK 954

THE ETIOLOGIC RELATION OF ACHYLIA GASTRICA TO COMBINED SCLEROSIS OF THE SPINAL CORD: THE RELIEF OF SYMPTOMS FOLLOWING ADEQUATE HYDROCHLORIC ACID THERAPY. DOUGLAS VANDERHOOF, M.D., RICHMOND, VA. 958

BOOK REVIEWS 972